



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 59

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 59

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

Volume 59 consists of four chapters. The first is by M. J. Silvester (Aldrich Chemical Co. Ltd.), and deals with polyfluoroheterocycles, updating the review by Chambers and Sargent which appeared in Volume 28 of *Advances in Heterocyclic Chemistry* in 1981. It covers mainly six-membered ring heterocycles and complements a review by Bürger that will appear in Volume 60 of our series and will cover fluorine-containing five-membered heterocyclic rings.

The second chapter is by E. S. H. El Ashry, N. Rashed, M. Taha, and E. Ramadan of Alexandria, Egypt. They contribute the first of a two-part essay on fused 1,2,4-triazines. The present chapter deals with triazines fused to heterocycles with three-, four-, and five-membered rings. In a subsequent volume of the series we will cover triazines condensed with six-membered and larger rings.

The third chapter is by J. Kuthan, P. Šebek, and S. Böhm of the Institute of Chemical Technology (Prague, The Czech Republic). It discusses developments in the chemistry of thiopyrans, selenopyrans, and teluopyrans since 1983 and thus updates Kuthan's own chapter in Volume 34 of *Advances*, published in 1983.

The final chapter is by M. R. Grimmett of Otago, New Zealand, and is the third and final part of his survey of the halogenation of heterocyclic compounds. It deals with the halogenation of condensed heterocycles. The first two parts of this series appeared in Volumes 57 and 58 of *Advances*.

A. R. KATRITZKY

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Recent Advances in Fluoroheterocyclic Chemistry

MICHAEL J. SILVESTER

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I. Introduction

This review covers the literature from 1981 to date. It is intended to update the review of Chambers and Sargent (81AHC1) on polyfluoroheterocyclic chemistry as well as bringing out other aspects of fluoroheterocycles. The synthesis of fluorine-containing five-membered rings will only be briefly described, as it will be discussed in detail in the review by Burger (94AHC). Reviews on fluorinated pyridazines (88MI1), penicillins and other β -lactams [92JFC(56)109], and benzimidazoles [92JFC(56)1] have been published during this period.

II. Synthesis

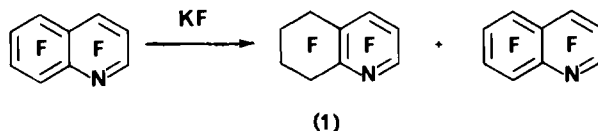
This discussion is separated into three sections depending on whether fluorine, or polyfluoroalkyl group, is introduced into a heterocycle or whether the heterocycle is formed from fluorinated synthons. Methods of introduction of fluorine into N-containing heterocyclic compounds have been reviewed (90CLY959).

A. INTRODUCTION OF FLUORINE INTO A HETEROCYCLE

1. Nucleophilic Halogen Exchange

Halogen exchange continues to attract attention although primarily in patent literature (88USP4746744) with the aim of increasing selectivity and reducing the severity of the reaction conditions. Phase transfer catalysts, such as Ph_4PBr , have been used to enhance the reactivity of KF (87TL111). Incompletely fluorinated material is recycled; however, if this is the target then overfluorinated material is wasteful. Chromium trioxide has been used to exchange halogens in mixture of chloro- and fluoropyridines in an attempt to overcome this problem [91JFC(53)33].

Reaction of KF with heptachloroquinoline and -isoquinoline at elevated temperatures gave partially saturated products, e.g., (1), as well as the expected perfluoroazaaromatics. It was proposed that the former arose from F^- exchange on products obtained by addition of traces of Cl_2 to the ring [86JFC(32)403].



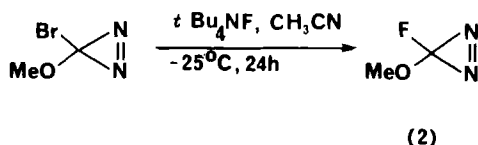
Halogen exchange in a flow system was necessary in order to reduce decomposition and improve yields for trifluoro-1,2,4-triazines [82JCS-(P1)1251] and -1,2,3-triazines (88T2583).

4-Fluorocoumarins (91S937), hexafluoro-1,8-diazabiphenylene [90-JCR(S)172], and decafluorotetrahydrobenzo [1,2-c:4,5-c']difurans [91-JFC(51)131] are obtained by KF exchange on their chloroanalogues.

The fluorination of tetrachloropyrimidine, 2,4,6-trichloropyrimidine, and trichloro-1,3,5-triazine with KF has been compared [81JFC(17)385]. An experimental and theoretical study of fluoride ion on 2,4,5-trichloro-6-methylpyrimidine has been reported [87JFC(35)373].

2,4-Difluoropyrimidines can be obtained by a method that obviates the need for using silver (II) fluoride in an autoclave. The approach is assisted by the enhancement of reactivity of F^- by use of a crown ether (85JHC149).

Halogen exchange of F^- is usually with chloro compounds; however, replacement of bromine has enabled fluorodiazirines to be obtained (83JA6513; 86TL419). Diazirine (2) was previously obtained by a difficult route involving F_2 . The relative ease of access to (2) enables a carbene whose reactivity is intermediate between that of electrophilic ($:CF_2$) and nucleophilic ($:C(OMe)_2$) carbenes to be studied.



2. Substitution of Hydrogen by Fluorine

The development and application of fluorinating reagents, old and new, have continued apace with much impetus derived from the interest in ^{18}F chemistry and high stability fluids. Fluorination in organic synthesis has been reviewed (86CRV997).

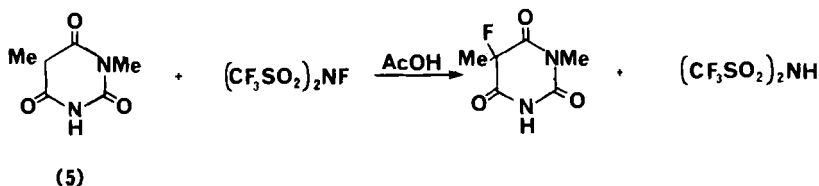
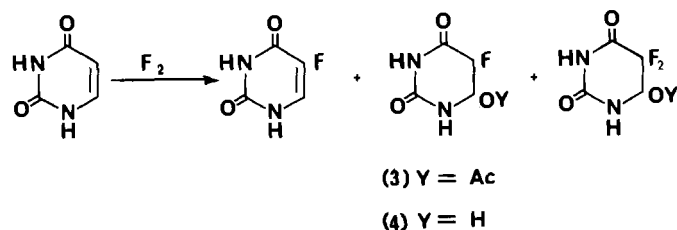
Direct fluorination of five-membered heterocycles gave products that were dependent on the heterocycle. For example, pyrrole yielded tar, whereas there was predominantly syn 1,4- addition of fluorine to furan (90G749).

With pyridine and its alkyl derivatives, and in contrast to chlorination, substantial nuclear fluorination occurred before the side chain was attacked (87TL255). Direct fluorination of isoquinoline was unsuccessful but 2-methylcarbostyryl gave the 4-fluoroderivative in 54% yield (82H429).

Fluorination of organometallics, e.g., Me_3Sn -imidazoles, has been used to improve selectivity with the aromatic—metal bond being broken preferentially (86BSF930).

Under carefully controlled conditions even complex molecules can be fluorinated. For example, the preparation of perfluoro-crown ethers (85CC1350) and perfluoro(2.2.2.)-cryptand (90JOC5933) has been described. Branched morpholines and piperazines have been directly fluorinated to their perfluoro analogues [90JFC(50)15].

A comparison of the reactivity of F_2 and $\text{CH}_3\text{CO}_2\text{F}$ with uracil, using ^{18}F as a tracer, revealed that apart from 5-F and 5,5-difluoro products, two others, (3) and (4), which depended on the solvent, were obtained. This dependency was believed to arise from the fate of the radical cation



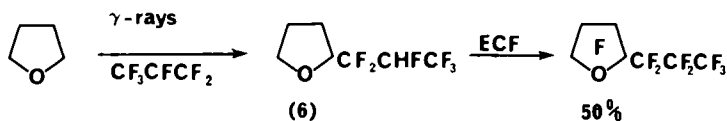
obtained by a single electron transfer with the fluorinating reagent [86JOC1466; 88JCS(P1)1203].

Antipyrine (86BSF861), bimanes (85JOC4152), and uracils and cytosines [86JOC1466; 88JCS(P1)2547] have been fluorinated using acetyl hypofluorite. With pyridine and quinoline no fluorination occurred and, instead, 2-acetoxy derivatives were obtained in high yield (87JA3789). Addition of a reactant, such as CH_2Br_2 or CH_2Cl_2 , competed with AcO^- through complexation and enabled selective chlorination and bromination of pyridine (88JOC1123). This suggests that acetyl hypofluorite has a wider role in synthesis than solely as a fluorinating reagent.

3-Fluoro-7-(dialkylamino)coumarins have been prepared in 15–30% yield by the use of XeF_2 or FCIO_3 (91KGS619). Fluorination of 2,4,6-pyrimidinetriones (5) with *N*-fluorobis-((trifluoromethyl)sulfonyl)imide gave 5-F derivatives in yields generally higher than that obtained by other methods (92JOC4281).

Fluorination of pyridine (90TL775), uracil (90T3093), and octaethylporphyrin [88JCS(P1)1735] has been described using cesium fluorooxysulfate. The outcome of the former was strongly dependent on the solvent. For example, with pyridine in methanol no fluorination was observed and 2-methoxypyridine was obtained. 2-Fluoropyridine was isolated when cyclohexane was the solvent (90TL775).

Electrochemical fluorination is an important technique for obtaining saturated perfluoroheterocycles. Incorporation of a partially fluorinated group into hydrocarbon ethers enhances their stability toward fluorination with CoF_3 and this approach has been extended toward electrochemical fluorination [89MI1; 90JFC(49)409]. Adduct (6) obtained by free radical



addition to hexafluoropropene was perfluorinated with surprising efficiency [90JFC(49)409].

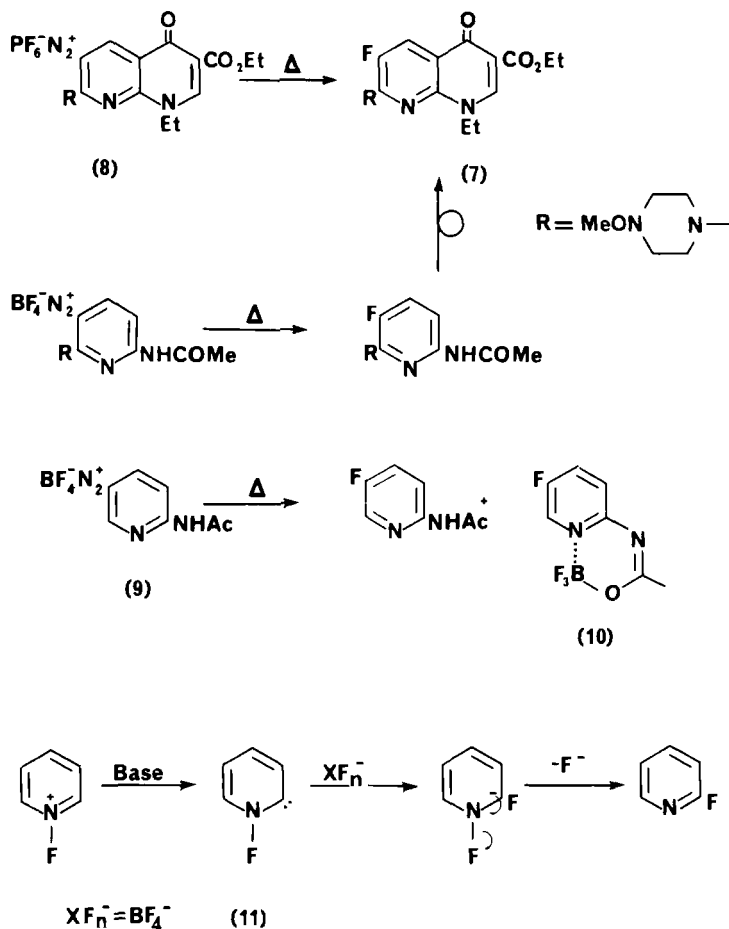
Electrochemical fluorination of morpholine and piperidine derivatives [91JFC(51)53] piperazine and diazepines (86NKK1249), and cyclic aminoethers [91JFC(52)317] have been reported. Yields are variable and side products result from ring contraction, fragmentation, and rearrangements. Several mechanisms have been proposed to explain electrochemical fluorination. A study of dimorpholine and dipiperidine derivatives has shown that the products obtained can be accounted for on the basis of a steric model [91JFC(51)53]. Electron transfer occurs to a C—H bond, weakened by HF, followed by attack of F^- on the positive center, leading to C—F bond formation. Further fluorination at this carbon is favored and repetition leads to perfluorination. The importance of the conformation in the anode layer is well illustrated by dimorpholine propane being perfluorinated in good yield (28%) with no side products. In contrast, increasing amounts of ring-contracted products are obtained with dipiperidines [91JFC(51)53].

Electrochemical fluorination of cyclic 2-(dialkylamino)-propionic acids provides a general route to optically active perfluoro-(2-cyclic(dialkylamino)-propionic acids [91JFC(52)133], which are a source of perfluorinated vinylamines (88CL1887).

3. Substitution of Other Groups

The Balz–Schiemann reaction continues to attract attention, with much of it generated by the interest in fluoroquinolones, e.g., (7), which is a potential antibacterial. Two approaches to its synthesis are possible—introduction of fluorine prior to or post ring construction. Decomposition of the tetrafluoroborate salt was unsuccessful, whereas the PF_6^- salt (8) gave only a poor yield (84JMC292). A more successful approach was the introduction of F into the pyridine nucleus prior to formation of the 1,8-naphthyridine ring (84JHC673). A comparison of decomposition media showed that cyclohexane was the best with regard to yield and time.

An unusual difluoroboryl imidate (10) was isolated during decomposition of (9) and its stability arose from a strong intramolecular bond between the pyridine N and boron. Formation of the desired 2-amino-5-fluoropyridine followed by the use of aqueous sodium hydroxide (89S905).



4-Fluoro-2-pyridone was prepared by a Balz–Schiemann reaction on 4-amino-2-methoxypyridine followed by $\text{Me}_3\text{Si} \cdot \text{BF}_4$ as counterion gave a better yield than PF_6 (85JHC145).

There are several reports on the decomposition of diazonium salts, in particular from pyridines, in anhydrous HF [81JFC(18)497; 88JFC(38)435]. Mildness of conditions and improved yields are benefits. The “elusive” 4-fluoropyridine can be obtained using this method [81JFC(18)497].

Nitrosonium tetrafluoroborate has been proposed as an alternative to $\text{NaNO}_2/\text{HBF}_4$. 2-Fluoropyridine is obtained in 69% yield on warming a CH_2Cl_2 mixture of NOBF_4 with 2- NH_2 -pyridine (90EUP430434).

Photochemical modification of the Balz–Schiemann reaction has enabled fluorine-containing biologically important molecules e.g., imidaz-

oles, to be obtained that would otherwise be unstable under the usual conditions (84JOC1951). Fluorinated pyrroles can be obtained in a similar manner, enabling 1,3,5,7-tetrafluoroporphyrins to be synthesized (85TL4221).

A novel route to 2-fluoropyridines involved the base-induced decomposition of substituted *N*-fluoropyridinium salts. Abstraction of the 2-H produces a singlet carbene (11) that removes F from a counterion. This is in contrast to the reaction with C nucleophiles, which are fluorinated, and is attributed to the high stability of C—F compared to O—F and N—F (89JOC1726).

4. Saturation–Rearomatization

High-valency metal fluoride fluorination of pyridine [82JFC(21)171], quinoline [82JFC(21)413], and 2-methylfurans [91JFC(51)179] has been reported. With 2-methylfuran a complex mixture of stereoisomers of partially fluorinated oxolans was obtained. These can be dehydrofluorinated to fluorooxolens and no furans have been observed. Conformation and structural group were found to influence the direction and readiness toward dehydrofluorination [91JFC(52)165].

Perfluoropyrrolidines rearranged to polyfluoropyridines, albeit in low yield, over iron gauze, at high temperature, but not with glass. The mechanism was believed to involve ring opening and ring closing as substituents appeared in the 2-position [81JFC(17)403].

B. INTRODUCTION OF A POLYFLUOROALKYL GROUP

By far the most important polyfluoroalkyl group is the trifluoromethyl and a review of trifluoromethylation and related reactions has appeared (91BGJ2255).

The coupling of a halogenated heterocycle with a polyfluoroalkyl halide, in the presence of copper, as a route to polyfluoroalkyl products has been well studied. In general, iodide is more reactive than bromide and an organocopper intermediate, such as CF_3Cu , is proposed. The formation and reactions of CF_3Cu have been reviewed (92T189). Common side products arise from reduction and the introduction of higher chain R_F groups, the latter arising from decomposition of CF_3Cu to $:\text{CF}_2$ followed by insertion.

Although iodides are more reactive than bromides, 2-(trifluoromethyl)pyridine was obtained in 95% yield from 2-bromopyridine and CF_3Br using an undivided electrochemical cell, DMF, and a sacrificial copper anode. CF_3Cu was the reactive intermediate (92CC53). Photochem-

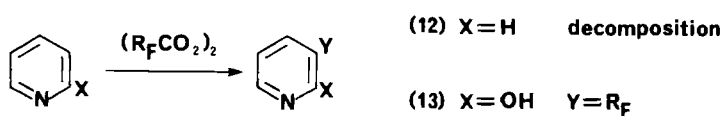
ical trifluoromethylation using CF_3Br gave low yields and conversions with heteroaromatics [88BCJ3531].

Sodium trifluoroacetate-copper(I) iodide has been used with a variety of heterocycles [81CL1719; 88JCS(P1)921]. Yields are lower than with benzenoids and probably result from coordination of the copper(I) species to the heterocycle. Indeed, addition of a coordinating ligand caused inhibition of reaction and decarboxylation of NaOCOCF_3 . Trifluoromethylation was facilitated by electron-withdrawing groups and $(\text{CF}_3\text{CuI})^-$ was proposed as a reactive intermediate. Use of sodium pentafluoropropionate enabled the introduction of C_2F_5 [88JCS(P1)921].

Copper coupling of bromoheterocycles with $\text{C}_6\text{F}_{13}\text{I}$ occurred in DMSO. Pyridines and pyrimidines gave good yields but with furans and thiophenes polysubstitution, reduction, and coupling through copper/bromine exchange was a problem [90JFC(46)137]. Yields were higher than those obtained using DMF [85JFC(27)291].

The dibromodifluoromethane-Cu-dimethylacetamide system can be used with chloroaromatics, although activating groups are required. Mixed success was achieved with heterocycles because of the increased tendency of CuCF_3 to decompose leading to higher perfluoroalkylated products [88CC638; 90JFC(50)411].

Usually control of chemo- and regioselectivities in radical reactions is difficult due to the high reactivity of R_F radicals. Thermolysis of $n\text{-C}_{10}\text{F}_{21}\text{I}$ in the presence of furan was successful but gave a mixture of isomers with pyridine [81JFC(17)345]. However, with bis(perfluoroalkanoyl)peroxides and electron donors, the R_F radical is formed, by electron transfer, in close association with the substrate radical cation in the solvent cage. The R_F group is thus introduced selectively. The ionization potential and nucleophilicity of the heteroatom lone pair determined whether perfluoroalkylation with bis(perfluoroalkanoyl)peroxides was applicable, e.g., (12) and (13) [88BCJ3549; 89JCS(P1)909; 90JFC(46)423]. CF_3 , C_3F_7 , and C_8F_{15} could be introduced, although trifluoromethylation was more difficult because the peroxide was more readily attacked by nucleophiles [90JFC(49)1].



Aminopyridines can be perfluoroalkylated in a photoinduced electron transfer process. A charge transfer complex between the heterocycle and polyfluoroalkyl iodide, observable by NMR, is photolytically stimulated

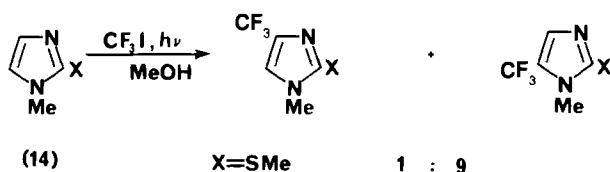
to cause single-electron transfer, generating a radical cation that couples with the R_F radical [92JCS(P1)1443].

Direct perfluoroalkylation of heteroaromatics occurs with R_FI when sodium hydroxymethane sulfinic acid (Rongalite) is present. 3-Perfluoroalkylcoumarins can be obtained (90CC1781). The distribution of isomers from substituted pyridines is compatible with a radical reaction (90TL2711).

A combination of xenon difluoride and CF_3COOH can trifluoromethylate appropriate substrates by free radicals arising out of the decomposition of xenon(II) trifluoroacetate (88JOC4582).

Formation of R_F radicals can occur by the electrochemical reduction of R_FI in aprotic solvents. Fission of the carbon—iodide bond occurs through a concerted one-electron transfer and competition follows between reaction to yield C-alkylated products or H abstraction. It has the advantage over photochemical methods in that it can occur in the presence of electron-withdrawing groups such as NO_2 . Application of electrochemically induced aromatic anion radicals is favored from a practical viewpoint (90TL277). An $S_{RN}1$ mechanism is proposed in the regioselective high-yield formation of 4-perfluoroalkylated imidazoles by reaction of R_FI or R_FBr with an imidazole anion (87CC1240).

Photochemical trifluoromethylation of imidazoles and its derivatives has been achieved using CF_3I in methanol (82JOC2867; 84JOC1060). 2- R_F and 4- R_F imidazoles were obtained but extension to other N-heterocycles was not as successful. Initial addition of CF_3 results in a σ -complex with electron-donating groups facilitating reaction and the substitution pattern consistent with the electrophilic nature of the R_F radical. A novel extension of the method was the use of methylthio groups (14) to increase electron density, hence reactivity, and limit sites available for attack. The group could easily be removed by hydrogenolysis (84JOC1060).



Azaaromatics can be perfluoroalkylated selectively in the 2-position using $RLi-BF_3$ in a Ziegler–Zeisser-type reaction. The BF_3 was essential as a promoter and other Lewis acids were found to be less effective.

Pyridines gave poor yields, whereas quinolines and pyrimidines were successfully perfluoroalkylated (91T6231).

Perfluoroalkylphenyl iodonium trifluoromethanesulfonates are effective as cationic perfluoroalkylating agents at introducing R_F into electron-rich heteroaromatics such as furan and pyrrole (81CL1663). Generation of CF_3^+ , itself, by γ -radiolysis of CF_4 in the gas phase has enabled the study of its reaction with five-membered heteroaromatics (91JA4544). Addition of chlorotrifluoromethyl diazirine to pyrrole followed by ring expansion gave 3-trifluoromethylpyridine in 35% yield [81JFC(18)533].

A powerful method of introducing a CF_3 group into aromatics is the conversion of CO_2H with SF_4 . The use of SF_4 with heterocyclics is not as widespread but it has been applied to imidazoles [81JFC(17)179], thiazoles, isothiazoles [91JFC(55)173], and furans (86BSF974).

C. FORMATION OF A HETEROCYCLIC RING FROM FLUORINATED PRECURSORS

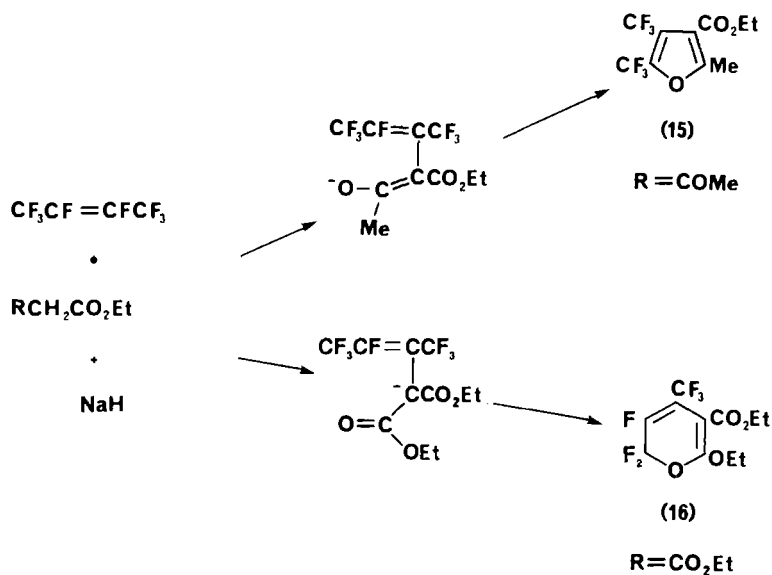
An alternative to the introduction of F or R_F is to synthesize the heterocycle from precursors that already contain the fluoro fragment. The discussion is separated into three sections, depending on the nature of the precursor.

1. *Fluorinated Alkenes, Allenes, and Alkynes*

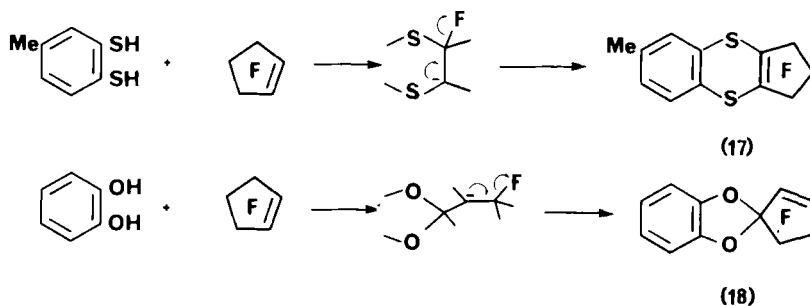
Fluorinated alkenes and alkynes are highly activated toward nucleophilic attack and reaction with bifunctional nucleophiles is a fruitful area for the synthesis of heterocycles. A review on perfluoroalkyl(aryl)acetylenes contains many examples (91RCR501).

Enolate anions substitute cyclic and acyclic fluoroalkenes to yield, among others, furans (**15**) and pyrans (**16**) [81JFC(18)213; 83JCS(P1)1235, 83JCS(P1)1239; 91BCJ2255]. Observed differences in products result according to whether charge is localized on carbon or oxygen in anionic intermediates. With the least acidic precursor, a pyran is the principal product. Usually sodium hydride is the base but KF has also been used [81JFC(18)213].

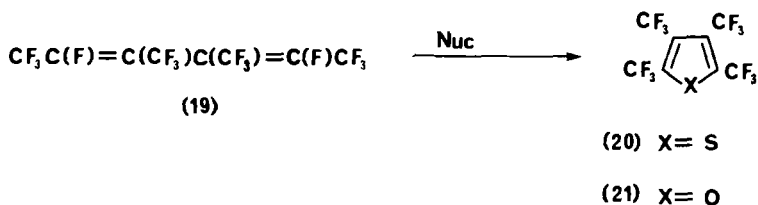
Perfluoro-2-methyl-2-pentene reacted with acyclic bifunctional nucleophiles such as 2-mercaptoethanol (89NKK1772) and ethylene glycol (86JAP61200983), in the presence of a base, to give 1,4-oxathiepin and dioxepin derivatives, respectively. Eight- and nine-membered heterocycles are obtained with 1,2-bifunctional benzenes such as salicylic acid [81JFC(18)447].



The reaction pathway of O-, N-, and S-containing 1,2-bifunctional benzenes with fluoroolefins depended on the relative abilities of the heteroatom to stabilize an adjacent anionic center, e.g., (17) and (18) [87-JCS(P1)763].

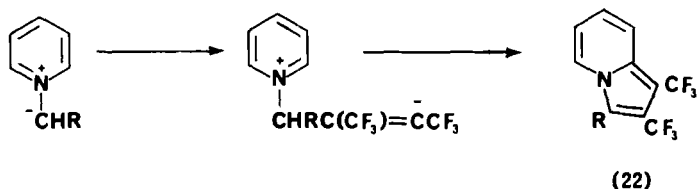


Highly fluorinated dienes were obtained in good yield by the sodium amalgam reduction of oligomers of perfluoroalkenes. These dienes are highly activated toward attack by nucleophiles and (19) is an excellent source of five-membered heterocycles (90CC1127). Alternative routes to (20) are by nucleophilic attack of S on hexafluorobut-2-yne [84JFC(25)47] and (21) by photolysis of perfluoro α -diazoketone in the presence of hexafluorobut-2-yne (87JOC2680).



Several papers have been concerned with the epoxidation of acyclic [83JFC(23)103; 84JCS(P1)1391] and cyclic fluoroalkenes [81IZV2612; 82JFC(20)243; 84JCS(P1)1391]. This can be carried out using aqueous NaOCl in acetonitrile and the lack of attack by OH^- shows the increased nucleophilicity of OCl^- over OH^- . These epoxides are remarkably stable as a result of the steric hindrance and electron withdrawal by the perfluoroalkyl groups. When attack does occur, it does so principally at the more substituted carbon [84JCS(P1)1391].

The mechanism of attack of 1,3-dipolar reagents on fluoroalkenes can be considered to be either stepwise or concerted. Heteroaromatic *N*-imines react by a stepwise 1,3 addition to perfluoroalkenes and -alkynes to give fluorinated pyrazolo[1,5-*a*]pyridines [82JCS(P1)1593]. Pyridinium *t*-butoxycarbonylmethylide with fluoroalkenes gave pyrrolo[1,2-*a*]pyridines [86JCS(P1)1769] and indolizines (22) are obtained with pyridinium phenacylide [91JFC(51)407].



Tetrafluoroallene reacted with the 1,3-dipolar reagent, *N*-phenylsydnone, to give a 4-trifluoromethylpyrazole, whereas tetrafluoropropyne gave a mixture of isomers. The difference in behavior was explained on the basis of frontier orbitals [82JCS(P1)2207].

Cycloaddition of tetrasulfur tetranitride to trifluoromethyl-substituted alkynes is a good route to 10π aromatic trithiadiazepines (87CC59). Cyclic nitrosofluoroalkanes undergo 1,2 addition to tetrafluoroethylene and 1,4 addition to hexafluorobuta-1,3-diene to give oxazetidines and oxazines respectively (84IC3654). Perfluoro(3,6-dihydro-2-methyl-2*H*-1,2-oxazine) is the product from the cycloaddition of hexafluorobutadiene to CF_3NO . This oxazine is readily attacked by nucleophiles to give predominantly

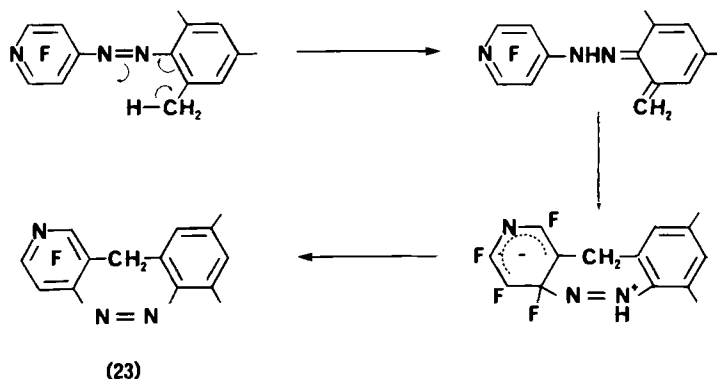
the 5-isomer with elimination of F and without migration of the double bond. An explanation based on negative hyperconjugation conferring a degree of aromaticity on the ring was proposed (86T6495).

Bis(trifluoromethyl)thiobut-2-yne is a source of CF_3S -substituted five- and six-membered heterocycles through pyrolysis, photolysis, and 1,3-dipolar cycloaddition (88CB1833).

2. Fluorinated Aromatics

Intermolecular ring closure from highly fluorinated aromatic precursors is an important route to many fluoroheterocycles and only a few illustrative examples can be given. A substantial amount of work has resulted from the interest in fluoroquinolones. In many instances the final molecule contains only a single F with the others having been utilized in the cyclization process and introduction of a side chain by nucleophilic substitution. A general review of fluoroquinolones and strategies for their synthesis has been published (90M11).

Fluorinated 1,2-diazepines (**23**) can be prepared by the thermolysis of 2,4,6-trimethylphenyl azo compounds with elimination of HF from the Me and F ortho to the azo linkage [84CC832; 88JFC(41)439]. The oxidation of these unsymmetrical diareno-1,2-diazepines gave *N*-oxides and diazepinones, depending on the oxidant [89JCS(P1)1117].

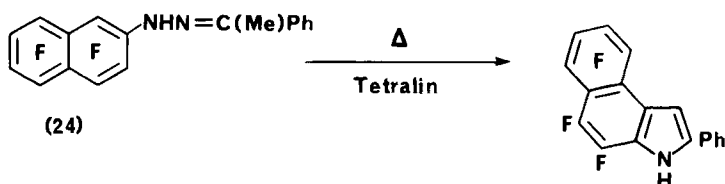


A useful route to 2,1,3-benzothiadiazoles is the F^- -catalyzed cyclization of 1-(4- $\text{X}-\text{C}_6\text{F}_4$)-3-trimethylsilyl-1,3-diaza-2-thiallenes [90JFC(50)359]. Fluoride ion catalysis is also used in the formation of heterocycles from pentafluorobenzoyl and -phenoxy compounds (81BCJ3447). Pentafluorophenylcarbonimidoyl dichloride with primary amines gave guanidines,

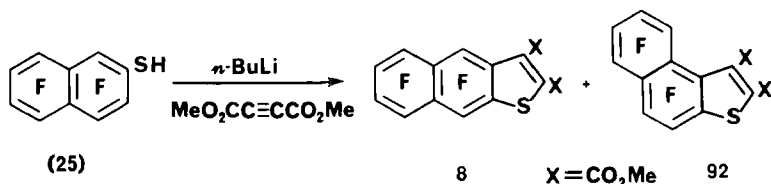
which cyclized on heating to tetrafluorobenzimidazoles (89JOU1523). Intramolecular dehydrofluorination is involved in the preparation of polyfluorodibenz[*b,f*][1,4]oxazepines from thermolysis of the respective *o*-hydroxybenzylideneanilines (86IZV477).

Intramolecular cyclization can yield fluorinated phenoxazines by a Smiles rearrangement (86IZV1855) and 2,3-dihydro-1,4-benzodioxins by a base-induced reaction [81JFC(18)483].

The uncatalyzed thermolysis of hydrazone (24) gave, among other products, an indole by loss of the *ortho* F in a mirror image of the usual Fisher indole synthesis [83JCS(P1)821].

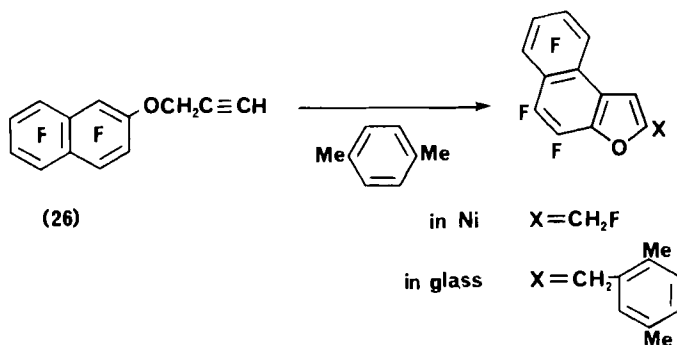


An opportunity to investigate the relative leaving ability of fluorine in the same molecule was presented by the intramolecular cyclization of (25) [89JFC(43)393]. It was found that there was a greater distinction between the two possible sites than when S (i.e., side chain $\text{CH}=\text{C}(\text{CO}_2^-)\text{S}^-$ [90JFC(50)229]) was the attacking nucleophile.



Polyfluoropyridyl- and pentafluorophenylprop-2-enyl ethers undergo a Claisen rearrangement and subsequent internal Diels–Alder addition on pyrolysis. In contrast, (26) followed a different reaction pathway, the outcome of which depended on whether it was carried out in glass or nickel. Under the conditions used, glass was found to be an effective Lewis acid whose activity could be inhibited by the addition of *N,N*-diethylaniline. A heterolytic, rather than homolytic, fission of the *ortho* C—F bond occurred concomitantly with cyclization, following the initial Claisen rearrangement [81JCS(P1)1417; 85JCS(P1)2643].

4,5,6,7-Tetrafluorobenzo[*c*]thiophene has been prepared by the reaction of *n*-BuLi on the benzyl methyl sulfoxide. It is more stable than its nonflu-



orinated analogue and undergoes Diels–Alder addition followed by elimination of S to give polycyclic fluoroaromatics [90JCS(P1)1919].

Cyclization of 2,3,4,5,6-pentafluorochalcones using $\text{NH}_4\text{OH}/\text{CH}_3\text{CO}_2\text{H}$ gave tetrafluoroquinolines [86JFC(32)457]. Fluorinated fused-ring 3H-azepines were formed in the thermolysis of polyfluoroanilines in the presence of acetophenone in tetralin [88JFC(40)109].

Hydroformylation of pentafluorostyrene was the first step in a five-stage synthesis of 3-Me-4,5,6,7-tetrafluoroindole. The methyl group was selectively converted to the $-\text{CHO}$ in 92% yield with SeO_2 (83TL-4573). 6-Trifluoromethylindole can be prepared from 2-bromo-5-(trifluoromethyl)nitrobenzene by Pd-catalyzed trimethylsilylethynylation and subsequent conversion to a dimethylacetal (86TL1653). 4,5,6,7-Tetrafluoroindole can readily be synthesized via F^- -catalyzed cyclization of 2-pentafluorophenylethylamine (89CJC1837).

3. Perfluoroalkyl-Containing Precursors

This section will consider only heterocycles containing a heteroatom in a six-membered ring, briefly mentioning where the synthon has a more general application. There is an extensive literature available and only illustrative examples can be given. A common feature of many approaches is the reversal or enhancement of reactivity arising out of the strongly electron-withdrawing effect of CF_3 . The use of hexafluoroacetone (87MI1), fluorinated β -ketoesters (85RCR1185), and trifluoromethyl-1,3-dipolar reagents (87YGK269) in fluoroheterocyclic synthesis has been reviewed.

a. *Containing One Heteroatom.* The addition of anilines to trifluoroacetyl acetylenes together with intramolecular acid-catalyzed cyclization allowed the regiospecific synthesis of CF_3 -quinolines. It was found that the orientation of substitution on the aromatic ring determined whether

the 4-isomer was formed exclusively (90TL2689). This precursor can also be used to prepare pyrazoles and isoxazoles in high yield (89TL2049). Perfluoroalkylalkynyl esters condensed with aniline followed by acid-catalyzed rearrangement to 2- R_F -4-hydroxyquinolines [81JFC(17)249]. 1-Trifluoromethylisoquinolines can be obtained from 5-benzoyloxy-4-trifluoromethyloxazoles by thermolysis and rearrangement (89CZ227).

Trifluoroacetimidoyl chlorides reacted with compounds containing an active methylene group to give enamines that thermally cyclized in cumene to 2-trifluoromethylquinolines (89TL4821). With *N,N'*-disubstituted trifluoroacetamides, the N-group determined whether cyclization gave triazoles or quinazolones (90TL2717).

Trifluoroacetonitrile is activated toward reaction with active methylene groups. Cyclocondensation with dialkyl 3-oxopentanedioates and 1,3-diphenylacetone gave 2,4-dialkoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylates (90JOC2964) and 2-(trifluoromethyl)-4(1*H*)-pyridinones (90JOC380), respectively.

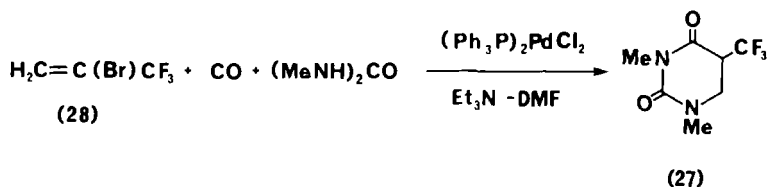
Trifluoroacetohydroximoyl bromide etherate is a synthon for thiadiazolines and oxadiazolines (87JHC1391). A fused isoxazolopyridine was obtained with excess malononitrile but, unexpectedly, dimeric malononitrile gave a highly substituted 2-(CF₃)-pyridine, albeit in 9% yield (87BCJ4480).

b. Containing Two Heteroatoms. The pyrimidine ring can be constructed from several synthons. α -Chloro- α' -trifluoromethylketone allowed the ready synthesis of 4-F-pyrimidines (91TL2467). 1-substituted perfluoroalkyl-1-alkenylphosphates behaved as synthetic equivalents of perfluoroalkyl-alkenyl ketones and reacted with amidine salts to yield 6-perfluoroalkyl-5-fluoropyrimidines (88CL819). Ethynyl perfluoroalkylketones can be trapped with amidinium salts to give 4-perfluoroalkylpyrimidines (90BCJ293).

Reaction of ethyl *N*-(cyanoacetyl)urethane with trifluoroacetonitrile gave 5-cyano-6-trifluoromethyluracil (85JOC4642). Trifluoroacetonitrile reacted with benzyl cyanide (86JOU1408) and diethyl malonate (89JHC7) to yield 2,6-bis(trifluoromethyl)pyrimidines. Cycloaddition of trifluoroacetonitrile with enamines having a β -H offered a general route to 2,4-bis(trifluoromethyl)pyrimidines (84LA991).

Dihydrouracils (**27**) can be obtained in one step by a palladium-catalyzed carbonylation of (**28**). The key intermediate is believed to be 2-trifluoromethylpropenoyl palladium (82TL4099).

Chlorotrifluoroethylene was converted in one step using *n*BuLi to diethylfluoromalonate, which was a useful precursor for 5-fluorouracil (84CL1573). Fluorinated pyrimidinones can also be obtained from α,β -unsaturated carboxylic acid derivatives prepared from 1-phosphonyloxy-perfluoroalkyl-1-alkenephosphonates (86TL2879).



Trifluoropyruvic acid hydrate is a useful starting material for the preparation of trifluoromethylated five-, six-, and seven-membered heterocycles with several heteroatoms. Its high reactivity, compared to its nonfluoro analogue, arises from the electron-withdrawing effect of the CF_3 group, leading to a highly reactive C center (88BSF944).

Quinoxalines are obtained when esters of 2-keto 3-fluoroacid derivatives (86BSF864) and 3,3-dicyano-2-(trifluoromethyl)acrylic acid [91-JFC(51)323] are treated with 1,2-phenylenediamine.

β -Chloro- β -(trifluoromethyl)acroleins reacted with 2-aminothiophenol at room temperature to give a mixture of a benzothiazole and quinoline. This was in contrast to the β -methyl analogue, which gave a benzothiazepine, the difference being due to the electronic influence of the CF_3 group (91TL643).

Perfluorobutan-2,3-dione [86JCS(P1)1043] and trifluoropyruvaldehyde (88JOC5088) are useful synthons for the preparation of heterocycles containing the bis(CF_3) pyrazine ring through condensation with 1,2-diamines. This enabled the extent to which 6- CF_3 and 7- CF_3 stabilized the covalent hydrate compared to the dehydrated products to be determined [86JCS(P1)1043, 86JCS(P1)1051].

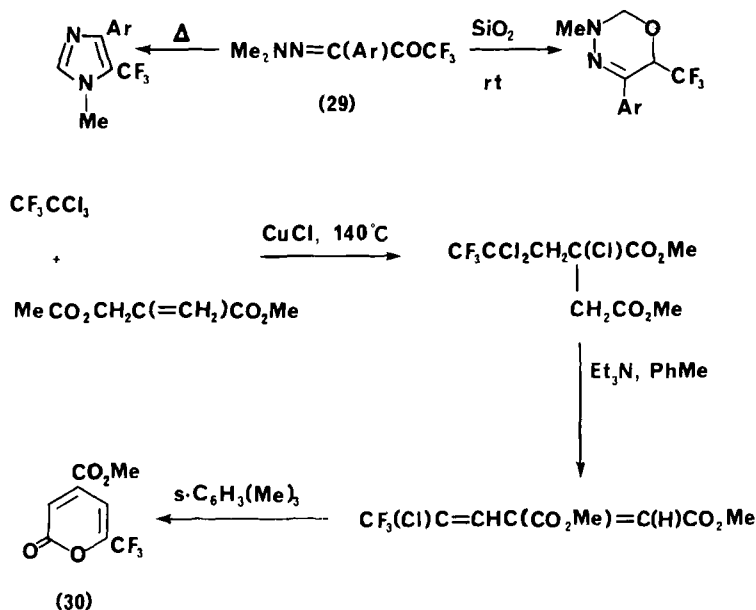
1,1-Di(cyano)-2,2-bis(trifluoromethyl)ethylene with 1,2-diaminobenzene gave a 1,5-benzodiazepine in 55% yield [90JFC1(47)59].

1,1,1-Trifluoro-2-nitrosopropene can be generated *in situ* from 1-bromo-3,3,3-trifluoropropan-2-one 2-oxime. It is a highly reactive nitrosoalkene that readily undergoes cycloaddition with silyl enol ethers and other dienophiles to give CF_3 -substituted 1,2-oxazines (92JOC339).

c. *Containing More than Two Heteroatoms.* Trifluoroacetylated hydrazones (29) cyclized to imidazoles (90JHC487) and/or oxadiazines (88S208), the outcome depending on the reaction conditions (88JOC129).

A novel use of a chlorofluorocarbon is in the synthesis of a pyrone (30) from 1,1,1-trichlorotrifluoroethane. The key step involves Cu(I) catalysis. Pyrone (30) is a useful CF_3 aromatic synthon, as it readily underwent (4 + 2) cycloaddition followed by spontaneous elimination of CO_2 (85-TL3947).

Triazines can be obtained either by condensation methods using the fluorinated anhydride (89IZV928) or by trimerization of nitriles, e.g., per-



fluoroheptanenitrile (87IZV1893). Methyl trifluoropyruvate with amidrazones gave 6-trifluoromethyl-1,2,4-triazines (88CPB3354).

Trifluoroacetonitrile oxide has been used in the synthesis of trifluoromethyl isoxazoles and isoxazolines (84BCJ2184; 86BCJ2631). In the presence of a base it dimerizes to a dioxadiazine (84JOC919).

Trifluoroacetonitrile underwent 1,3-cycloaddition with ylides to give triazolo[1,5-*a*]pyridine [82JFC(20)373] and imidazo[1,2-*a*]pyridines [86-JCS(P1)1769].

4,4-Bis(trifluoromethyl)-substituted 1,3-heterodienes are a rich source of heterocycles through cycloadditions, for example, with ketenes (86CZ83) and azirines [89JFC(42)51] to give dioxazines and triazepines, respectively.

III. Properties and Reactions

A. INDUSTRIAL APPLICATIONS

Fluorinated heterocycles have many uses and the following are some typical examples. Trifluoromethyl pyridines are useful building blocks for agrochemicals (91MI1). Fluorinated quinolones have evoked considerable interest in the last 10 years as antibacterial agents (90MI1, 90MI2). The

ease of displacement of fluorine from polyfluoroheterocycles has created a lot of interest in their introduction into fiber-reactive dyes (90MI3). A new class of fluoropolymers based on the bis-2,2-(trifluoromethyl)-4,5-difluoro-1,3-dioxole structure offers the usual properties expected from fluoropolymers together with good optical clarity and high glass transition temperature (90MI4). (Perfluorohexyl)thiirane is a new precursor of fluorinated surfactants [90JFC(49)159].

B. NUCLEOPHILIC SUBSTITUTION

1. Nucleophilic Aromatic Substitution

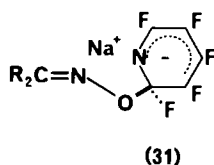
Polyfluorinated azaaromatics are highly activated toward nucleophilic aromatic substitution and much work has gone into understanding the factors that influence reactivity and patterns of substitution. The activating influence of ring N has been determined and found to activate positions o : m : p— 6.2×10^4 : 8.5×10^2 : 2.3×10^5 , respectively [82JFC(20)507]. A study of the kinetics of substitution with NH_3 in dioxan and MeONa in methanol was aimed at separating the activating effects of *ortho* and *meta* fluorine. It was concluded that the *ortho* activation arises out of a combination of ion-dipole interactions and the stabilization of the ionic σ -complex [88JCS(P1)255]. The general kinetics of nucleophilic aromatic substitution in polyfluorinated compounds has been reviewed [90JFC(47)361]. The kinetics of acid-promoted hydrolysis of 2-F-pyridines, -quinolines, and -pyrimidines has been studied (81JOC4363; 87JOC5194).

Nucleophilic aromatic substitution of pentafluoropyridine continues to hold interest. The following illustrate the diversity: the indole anion (88JOU2344), organosilicon reagents (90JOU187), potassium *t*-butoxide [88JCS(P1)3301], pyridinium phenacylide [91JFC(53)127], pyridinium *t*-butoxycarbonylmethylide [82JFC(20)127], *N*-iminopyridinium ylide [82JCS(P1)1593], aromatic sulfone anions [85JFC(27)237], 2,5-bis(trifluoromethyl)triazolate anion [90JFC(48)149], sodium diethylnitroxide [89JFC(44)441], and sodium [bis(trifluoromethyl)aminooxy] [88JFC-(38)217]. Nucleophilic substitution of trifluoro-1,2,4-triazine [82JCS-(P1)1251] and 2,4-difluoropyrimidine (85JHC149) has also been studied.

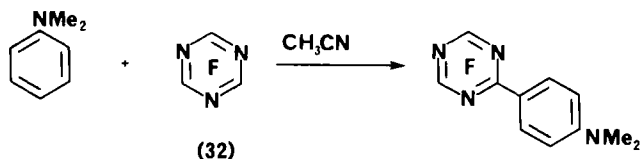
Introduction of the CF_3S group into electron-rich heteroaromatics can be achieved using CF_3SCL , e.g., pyrrole [82JFC(19)461] and indolizines [81/82JFC(19)67]; however, this is not possible with perfluoroazaaromatics. The ready generation of CF_3S^- from thiocarbonyl difluoride allows access to CF_3S -substituted products by reason of their activation toward

nucleophilic aromatic substitution [87JCS(P1)2119; 88JCS(P1)1179]. A variation in reactant ratios enables 1 : 1, 2 : 1, and 3 : 1 adducts to be readily obtained with tetrafluoropyridazine. Substitution with pentafluoropyridine occurs at the 4 position, with further attack being determined by thermodynamic and kinetic control reminiscent of perfluoroalkylation reactions with carbanions.

Until recently the substitution pattern in pentafluoropyridine was considered to be $4 \gg 2$; however, several examples have been found where substitution at the 2 position occurs to a greater extent than expected, for example, with sodium oximate. That ring N was an essential feature was shown by the comparison with octafluorotoluene, which gave the expected product (89CC1268). An association between the ring N, the cation, and anion in the solvent accounted for the high percentage of the 2-isomer (31). Other nucleophiles, e.g., LiN^iPr_2 , also gave a higher than expected 2-isomer [88JCS(P1)3301].



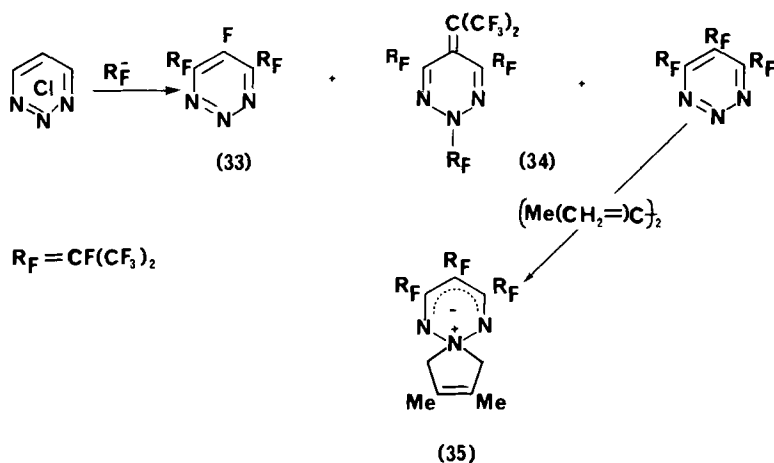
Aromatic amines can act as carbon nucleophiles with highly activated perfluoroalkyl- or trifluoro-1,3,5-triazines (32). Less reactive fluoroazaaromatics either required more forcing conditions or only a weak complex was formed as in the case of pentafluoropyridine. Ortho and para electron-donating groups in the aromatic ring of the amine caused substitution through the N of the aniline, and dealkylation was observed (92T7939).



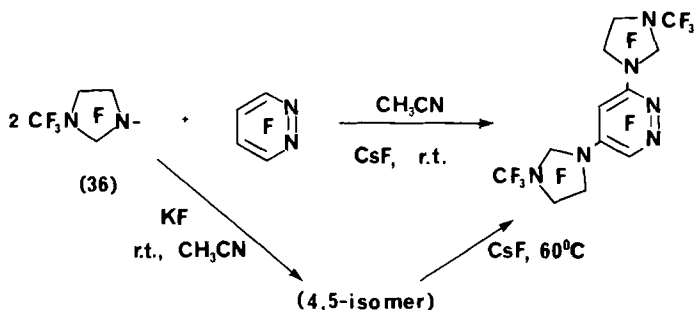
2. Fluoride Ion-Induced Reactions

Fluoride ion-catalyzed polyfluoroalkylation is a powerful method for introducing R_F groups into polyfluoroazaaromatics. Trichloro-1,2,3-triazine is such a reactive system that fluorination and polyfluoroalkylation

can be carried out simultaneously. Compound (33) formed an observable anion with CsF, an observation of practical value, since KF, which did not, led to a mixture of products. Product (34) is unusual. It was the only product when the reaction was carried out at higher temperatures and is a rare example of nucleophilic attack on a ring N. Further examples are shown by reaction with Grignard reagents and electron-rich alkenes. With 2,3-dimethylbutadiene a zwitterion (35) was formed in high yield by cheletropic addition (87CC1697; 88T2583).



The use of nitrogen anions in this process has not been well investigated. Nitrogen anion (36) readily substituted fluorine in perfluoroazaaromatics and the products could be rationalized on the basis of kinetic and thermodynamic control. With tetrafluoropyridazine and CsF as a source of F^- , none of the expected 4,5-isomer was obtained. For 4,5 substitution a less



active source of F^- , i.e., KF, was required. In general for anions of low stability, kinetic control predominates, whereas for stable anions thermodynamic control is important [86JFC(32)389]. Nitranion (36) belongs to the latter class, with an anion being observed with ^{19}F NMR [85JCS(P1)53]. The 4,5-isomer can readily be converted to the 3,5- using CsF and a higher temperature [86JFC(32)389].

The reaction with 4-nitrophenol and pentafluorophenol in the presence of KF-18-crown-6 has been investigated. Pentafluorophenoxide anion was found to be a better leaving group [82JFC(20)439]. Alkali metal fluorides on graphite can act as catalysts for nucleophilic substitution of pentafluoropyridine [90JFC(46)57].

C. REACTION WITH ELECTROPHILIC REAGENTS

Pentafluoropyridine is less reactive toward addition of fluorine by BrF_2^+ than polyfluorobenzenes. The product is perfluoro-1-aza-1,3-cyclohexadiene (81JOU879).

Raman and multinuclear NMR spectroscopy have been used to study the reaction product of pentafluoropyridine with $XeF^+ AsF_6^-$ in anhydrous HF. Identified in the mixture was a fluoro(pentafluoropyridine)xenon(II) cation with the Xe bonded to the ring N (88CC257).

Reaction of tetrafluoropyrimidine with anhydrous HCl set up an equilibrium in which the outcome was determined by the reaction conditions. It allowed the isolation of 2,4,6-trichloro-5-fluoropyrimidine, an isomer not accessible by KF exchange. Hydrogenolysis and hydrolysis of the 2,5-difluoroisomer provided a convenient route to 5-fluorouracil [89JFC(45)417].

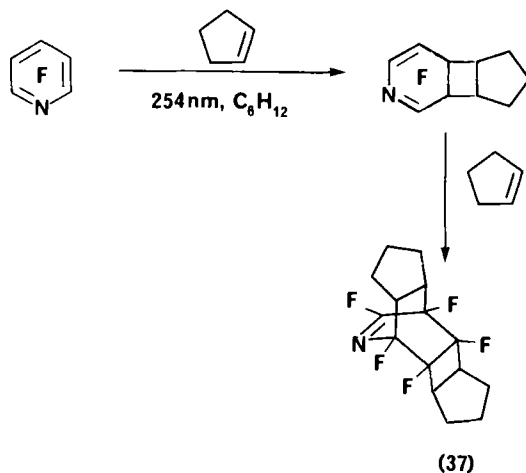
The α - CF_2 in perfluoro(*N*-alkylcyclic amines) can be hydrolyzed with oleum, and mercury sulfate as catalyst, to yield perfluorolactams [88JFC(41)213].

Superacid media, HF/ AsF_5 and HF/ SbF_5 , caused perfluorinated 1,2-oxazetidines to ring open by breaking the carbon heteroatom in preference to the N—O bond (89CJC1724).

The 4-chloropyrimidin-2-yl dichlorophosphate ester has been isolated in 58% yield as an intermediate in the chlorination of 6-(trifluoromethyl)uracil with $POCl_3$ followed by PCl_5 (83JHC219). The enhanced stability of this compound was believed to be due, in part, to electron withdrawal by the CF_3 group. Tri-*n*-propylamine was found to be the most effective in a comparison of the influence of bases on chlorination with $POCl_3$ (87JHC1243).

D. RADICAL AND ADDITION REACTIONS

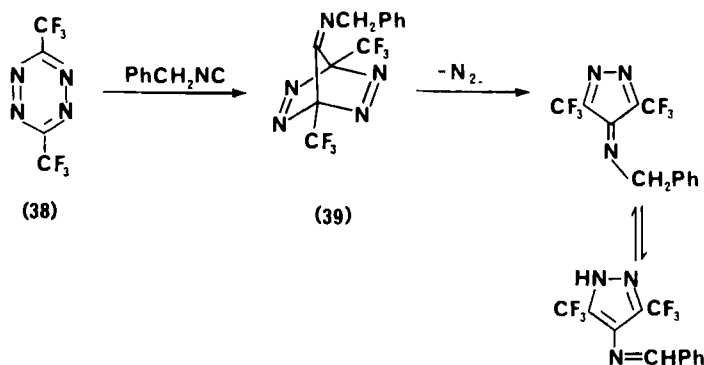
The photochemical [2 + 2] cycloaddition of cyclopentene to pentafluoropyridine in cyclohexane gave a 1:1 adduct, which in excess olefin gave a single 1:2 adduct (**37**) (82JOC4462). The solvent has an important role, as in its absence two 1:2 adducts are obtained. With $\text{PhC}\equiv\text{CR}$ in cyclohexane, the nature of R determined whether a triene ($\text{R} = t\text{-butyl}$) or tetraene ($\text{R} = \text{Me}$) was in the product mixture (89T1755). A mixture of 1:2 and two 1:1 adducts was obtained by [2 + 2] addition of but-2-yne in the absence of a solvent [87JFC(20)745].



Addition of cyclopentene to trifluoro-1,2,4-triazine gave products arising from addition of a second molecule of olefin. This was in contrast to trichloro-1,2,4-triazine where the eventual products were predominantly pyridine derivatives [82JCS(P1)1245].

Triazine (**38**) is ideal for inverse electron-demand Diels–Alder cycloadditions, for example, with azulene to give a 1,4-bis(CF_3)phthalazine (89CB711). A rare example of the synthesis of a five-membered heterocycle originating from [4 + 1] cycloaddition followed by [4 + 2] cycloreversion was reported using (**38**). The intermediate tetraazanorbornadienimine (**39**) is highly strained and eliminates N_2 [82AG(E)284].

5-Trifluoromethyl-1,3-dioxin-4-ones can act as the enone component in [2 + 2] or as dienophiles in Diels–Alder reactions and are potential synthons for enantiomerically pure trifluoromethyl aliphatics [92JCS-(P1)1393].



Diels–Alder cycloaddition of 3,4-bis(trifluoromethyl)furan with ethyl propynoate involved addition of two α,β -unsaturated esters followed by acid-catalyzed ring opening, rearrangement, and elimination of ethanol to give a 6,7-bis(trifluoromethyl)isocoumarin-3-carboxylate [92JFC(56)359].

6-Trifluoromethyl-1,2,4-triazines and 1,2,4-triazin-5-ones are versatile precursors for azetidines and pyridines by cycloaddition reactions. Enhancement of reactivity was observed through the presence of the trifluoromethyl group (88CPB3354).

Cobalt trifluoride fluorination corresponds to the electron-transfer mechanism via a radical cation. R_F groups attached to the ring enhance the stability of intermediate dienes and monoenes. Perfluoroalkyl pyridines, pyrazines, and pyrimidines were successfully fluorinated but pyridazines eliminated nitrogen. The lack of certain dienes was attributed to the difference in stability of $\text{FC}=\text{C}$ and $R_F\text{C}=\text{C}$ and steric effects [81JCS(P1)2059].

E. ORGANOMETALLICS

The lithiation of 2-F- and 3-F-pyridines has been investigated with different reagents and reaction conditions.

A useful approach to synthesis has been adopted using complementary activating groups. Directed lithiation of 2-F-pyridine with lithium diisopropylamide followed by iodination gave 2-F-3-I-pyridine. This can undergo nucleophilic $S_N\text{Ar}$ substitution at F followed by $S_{\text{RN}}1$ attack at iodine (88JOC2740). Lithiation of 2-fluoropyridine with $n\text{BuLi}$ –TMEDA–THF at -40°C enabled 2,5-dihydropyridines to be isolated (81JOC4494).

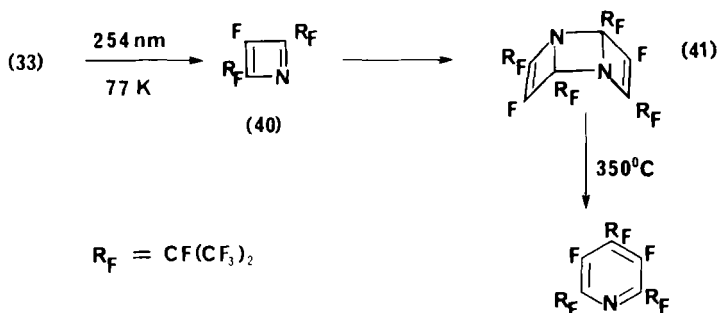
With 3-F-pyridine the conditions of metallation can be chosen to favor either 2- or 4- attack. In ether at -60°C the 2-Li derivative is the kinetic isomer, whereas at higher temperatures it equilibrates to the thermody-

namic 4-isomer, allowing access to 2,3- or 3,4-disubstituted pyridines (83T2009).

F. FRAGMENTATION AND REARRANGEMENT PROCESSES

Fluorine and perfluoroalkyl groups have great utility in the study of thermal and photochemical processes. The use of ^{19}F NMR as a structural probe and, in the case of R_F , the lack of migration make them particularly useful as labels. The enhanced stability of small ring structures containing R_F groups has made it an exciting area for investigation.

Recent work on the photochemistry of fluorinated 1,2,3-triazines has enabled the observation by IR and mass spectrometry of fluorinated azetes. 4π -antiaromatic species are of interest but more attention has been given to cyclobutadienes than azetes. Photolysis of (33) at 77 K gave azete (40), which on warming gave a quantitative yield of a 1,3-diazetidene (41). Thermolysis of (41) gave (via ring opening to a 1,5-diazocine) a pyridine whose structure confirmed the identity of (41). Azete (40) could also be trapped with furan, yielding three 1:1 adducts.



The efficacy of R_F in stabilizing small rings is well illustrated by the fact that the azete from trifluoro-1,2,3-triazine is considerably more reactive. Trapping experiments were unsuccessful and a polymer was isolated at room temperature. The dimer (41) forms an observable anion with CsF , which confirmed the endo structure [87CC1699; 90JCS(P1)975, 90JCS(P1)983]. In contrast, trifluoro-1,2,4-triazine is resistant to vapor phase photolysis and flow pyrolysis [87JCS(P1)1251].

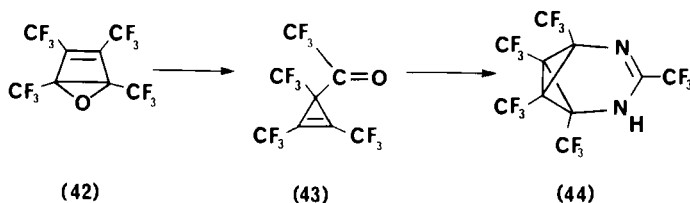
Trifluoromethyl-containing valence bond isomers have been reviewed (81ACR76).

The free radical catalyzed generation of valence isomers has been described to account for the products observed during the thermal re-

arrangement of perfluoroalkylpyridazines. Perfluoro(4,5-di-*s*-butyl)pyridazine was found to act as an efficient promoter for this process [81JCS(P1)1071].

Dewar furan (**42**) has been prepared by a multistage synthesis from its thiophene analogue. On thermolysis (**42**) gave (**43**) by fragmentation to a carbene followed by cyclization (82JA847). This is in contrast to the thiophene analogue, which undergoes rearomatization and can be understood on the basis of bond energy differences and the enhanced aromaticity of thiophene.

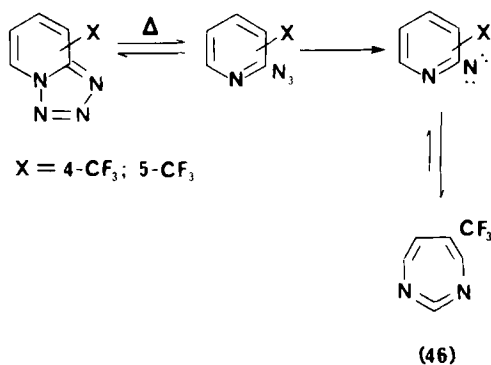
A valence bond isomer of pentakis-(trifluoromethyl)-1,3-diazepine (**44**) was prepared from (**43**) (81TL1113); (**44**) can be transformed thermally or photochemically to a 2,4-diazabicyclo(3.2.0)hepta-2,6 diene (**45**), which was subsequently photolysed to an imidazole in an anionic process. Compound (**45**) is highly acidic arising out of the bishomoaromaticity of the anion and forms a salt with Et_3N (81TL1369).



Photolysis of 2,3-bis(trifluoromethyl)thiophene gave an isomer mixture of 2,3- and 3,4-bis(trifluoromethyl) thiophenes and Dewar thiophenes. The 2,5- analogue gave 2,4-bis(trifluoromethyl)thiophene via an intermediate that was not the Dewar thiophene. This indicated that provided they are orientated correctly, two trifluoromethyl groups are sufficient to isolate a Dewar thiophene (84TL1917).

The steric and dipole-dipole effects of the CF_3 group on valence isomerization in the Dewar pyridine-azaprismane-pyridine system have been studied. These reveal themselves in the high stability, compared to the pyridine, of the valence isomer arising out of the large activation energy for rearomatization. The transformation of a 1-Dewar to 2-Dewar pyridine was observed (89T3115).

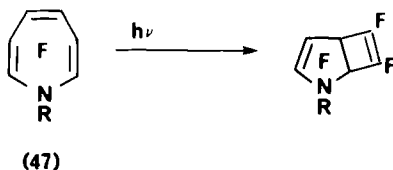
1,2-Dehydro-1,3-diazepines (**46**) were observed as products through the photolysis and the thermolysis of trifluoromethyl azido/tetrazolopyridines. The electron-withdrawing ability of CF_3 aids the tetrazole-azide tautomerism and facilitates nitrene reactivity. The lack of migration of this group was illustrated by the same dehydrodiazepine being formed



from two different isomers. This procedure offers a route to unknown cyano(trifluoromethyl)pyrroles (92CC1062).

6-Azido-4,5,7-trifluorindole was photolysed at -196°C in toluene to give the benzylic insertion adduct via singlet nitrene to triplet intersystem crossing. The results suggest that it may be useful as a photoaffinity label at this temperature (89TL6465). Thermolysis of 4-azido-2,3,5,6-tetrafluoropyridine in the presence of pentamethylbenzene gave a product derived from singlet nitrene insertion into the aromatic C—H [90JFC(47)527].

The Dewar benzene of hexafluorobenzene formed an adduct with phenylazide that gave a polyfluoro-1*H*-azepine on pyrolysis. $R=\text{CO}_2\text{Et}$ (47) was obtained when ethylazidoformate was decomposed in C_6F_6 [82JCS(P1)2101]. Photolysis of (47) yielded a 2-aza-bicyclo(3.2.0)hepta-3,6-diene, which, in contrast to its nonfluorinated analogue, showed excellent thermal stability (3 h, 200°C , 88% recovered) [82JCS(P1)2105].



2,5,6-Trifluoropyrimidin-4-ol lost its aromaticity under mild conditions using activated dimethyl sulfoxide and gave the 2,3-sigmatropic rearranged product with the MeSCH_2^- group on the 3-N [87JCS(P1)2091]. This was also the same site to which the propenyl ether group migrated in a 3,3-sigmatropic shift during the flash vacuum pyrolysis of allyl 2,5,6-trifluoropyrimidin-4-yl [86JCS(P1)515].

TABLE HETEROCYCLIC N-F REAGENTS

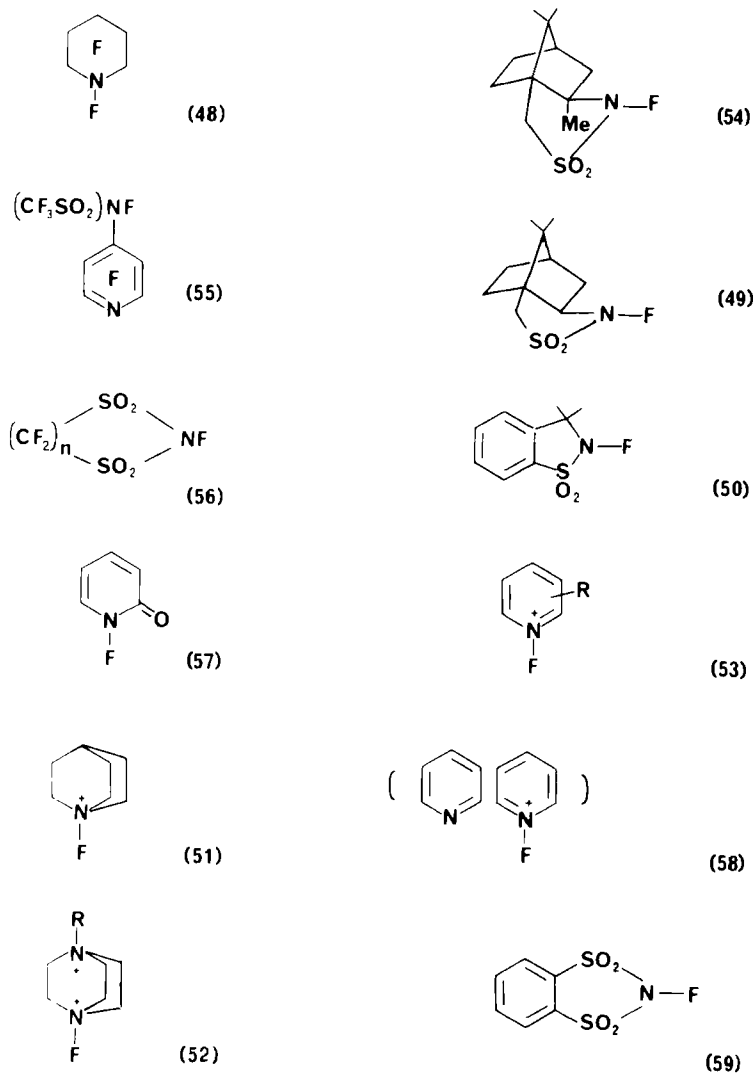


FIG. 1. Heterocyclic N—F reagents.

G. HETEROCYCLIC N—F REAGENTS

Over the last few years the number of heterocyclic N—F reagents has developed tremendously (Fig. 1). The driving force for this interest has been the need for easily accessible and safe reagents capable of the selective fluorination of bioactive molecules. Generated by reaction of F_2 with the parent compound, products are obtained that are capable of fluorinating species as diverse as carbanions and aromatics depending on their fluorinating power.

Compounds such as sultam (**49**) suffer from HF elimination as a major side reaction. Perfluoro-I-aza-I-cyclohexene is generated from (**48**) by loss of F^- and then competes with (**48**) for the nucleophile [91JFC(52)389]. This has led to the development of reagents where no α -H is present, e.g. (**50**) (89HCA1), or N is a bridgehead (**51**) [88JFC(41)287]. Variation in fluorinating strength can be achieved with reagents (**52**) (92CC595) and (**53**) (90JA8563; 91BCJ1081) by altering the substituent R. In the case of (**53**), electron-withdrawing groups increase effectiveness but reduce stability. Variation of R and counteranion can also influence selectivity (90JA8563; 91BCJ1081). Enantioselective fluorination is possible with N-fluorosultams (**49**) and (**54**) (88TL6087). A polymeric N—F reagent has been developed [86JFC(34)28]. Other reagents are (**55**) [90JFC(46)297], (**56**) (87JA7194), (**57**) (83JOC761), (**58**) (91JOC5962), and (**59**) (91TL1631).

Cyclic voltammetry and polarography have been used to study the mechanisms of fluorination and provide an indicator of their relative strengths [92JFC(59)157, 92T1595]. Two mechanisms have been proposed involving S_N2 or electron transfer, although it is likely that which is followed depends on the N—F reagent used.

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Condensed 1,2,4-Triazines: I. Fused to Heterocycles with Three-, Four-, and Five-Membered Rings

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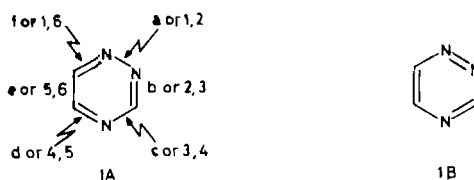
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I. Introduction

A large number of 1,2,4-triazines that are condensed with one or more heterocycles are well known and a wide variety of synthetic methods for their preparations are available. Compounds containing the 1,2,4-triazine moiety are in use as pharmaceuticals, dyes, pesticides, herbicides, etc., and a great number of reports have been directed to the synthesis of the title heterocycles having potentially useful biological properties.

Various reviews dealing with the 1,2,4-triazines have been published. The most recent is that published by Neunhoeffer and Wiley (78HC749) covering the literature through 1974. Owing to the increase of the number of publications on the 1,2,4-triazines, a survey of the literature on their condensed ring systems with three- to five-membered heterocycles, from 1974 through 1992, constitutes the subject of this review.

The parent compound of this series has two Kekule structures **1A** and **1B**. It may be fused with other heterocycles at its six different sites. The 1,2,4-triazine ring also may constitute a central unit in a condensed ring system where two or more faces are included in fusions. These are not included in this review. The arrangement of the literature follows the type of condensation: through two carbon atoms, carbon and nitrogen atoms, or two nitrogen atoms (78HC749). However, we found that the present review can be divided conveniently according to the type of heterocycle fused to the triazine ring and the order of increasing size of the heterocycle and the number of heteroatoms. Each type is subdivided according to the



SCHEME 1

nature of the fusion on the triazine ring. The site of fusion on the triazine ring may be indicated by a letter or by numbers, depending on the type of heterocycle fused to it. For example, the condensed ring systems may be named heterocyclo[x,y-z][1,2,4]triazines or [1,2,4]triazino[x,y-z]heterocycles where x and y are designated according to the numbers on the ring of the heterocycle in the former and the triazine ring in the second ring system, respectively. The letter z denotes the first part of fusion of the triazine ring in the former and represents the first part of fusion of the heterocycle in the second. Heterocycles having fused benzene rings are categorized according to the heterocycle that is directly fused to the triazine ring unless they are characterized by common names. The biological activity of the reported compounds are included under each ring system. Benzo[1,2,4]triazines have been reviewed (84MI3). (See Scheme 1.)

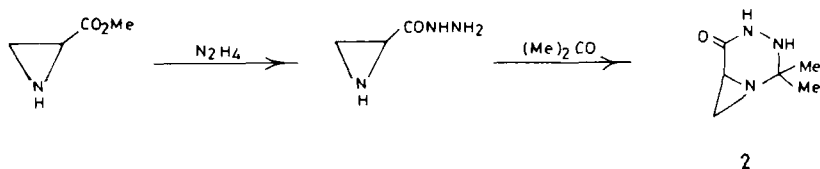
II. Azirino[1,2,4]triazines, Azirino[x,y-z][1,2,4]triazines, and Azirino[1,2-d][1,2,4]triazines

Only one report is concerned with the synthesis, molecular structure, and X-ray analysis of this ring system as **2** (86KGS477). The synthesis of **2** was achieved by the cyclization of 2-aziridine carboxylic acid hydrazide with acetone as shown in Scheme 2.

III. Azeto[1,2,4]triazines

AZETO[X,Y-Z][1,2,4]TRIAZINES

The fusion of a four-membered heterocycle with one heteroatom onto the 1,2,4-triazine ring may occur in six different ways. Each edge may give rise to one type of bicyclic ring system, except that edge **a** of **1A** could not form such a ring whereas edge **e** provides two different isomeric combinations. Only three such types have been published during the period of our review.



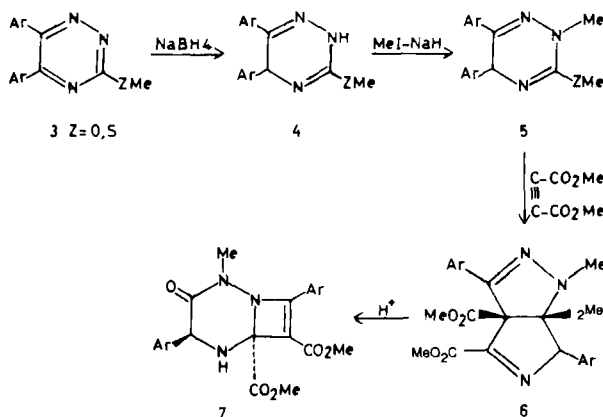
SCHEME 2

1. Azeto[1,2-b][1,2,4]triazines

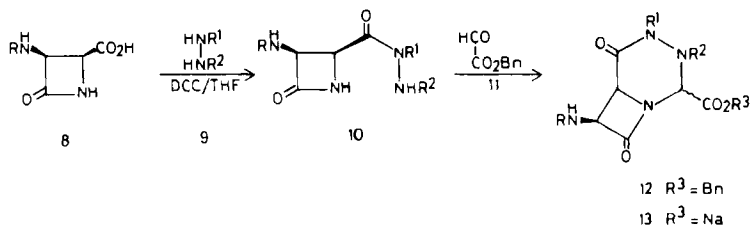
The synthesis was achieved by reduction of **3** with sodium borohydride to give dihydrotriazines **4** which were N-methylated to give **5**. Treatment of **5** with dimethyl acetylenedicarboxylate gave triazabicyclooctadienes **6**, which on treatment with acid afforded azetotriazine derivatives **7** (80JOC4587) (Scheme 3).

2. Azeto[1,2-d][1,2,4]triazines

Coupling of 3-substituted acetamido-4-oxoazetidine-2-carboxylic acid **8** with hexahydropyridazine or its analogues **9** gave **10**, whose subsequent condensation with benzyl glyoxalate **11** gave **12** as a mixture of epimers (77TL1855, 78USP4093807). The ester was then catalytically hydrogenolyzed with Pd/C in the presence of sodium bicarbonate to the respective carboxylate salt **13**. Some showed modest activity against *Staphylococcus aureus* and improved activity was noticed with increasing ring strain (Scheme 4).



SCHEME 3



SCHEME 4

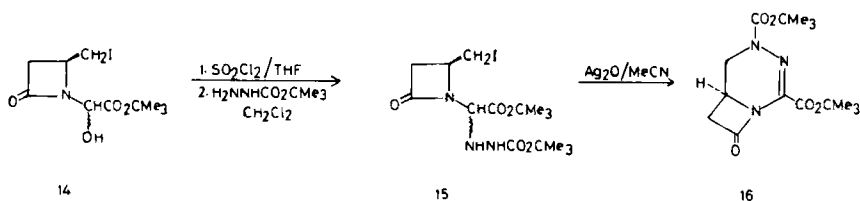
Sequential treatment of the azetidinone **14** with sulfonyl chloride and tert-butyl carbazate gave hydrazide **15** as a mixture of diastereoisomers, which on treatment with silver oxide in acetonitrile gave triazabicyclo[4.2.0]oct-2-ene **16** (84CC1289). The structure was established by X-ray crystallography. Analogues of **16** showed no significant antibacterial activity and did not act as an ampicillin synergist against β -lactamase-producing bacteria (Scheme 5).

3. Azeto[2,1-f][1,2,4]triazines

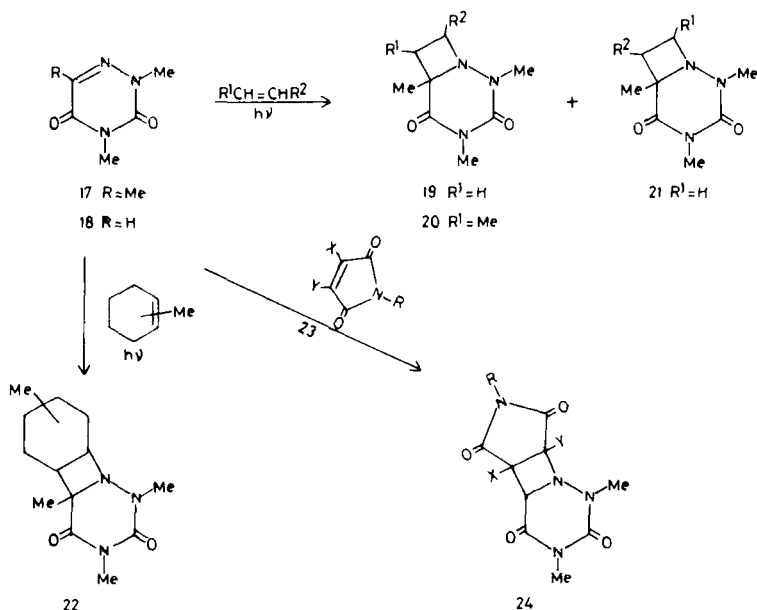
Azetidines **19** and **21** resulted (81MI2) from photocycloaddition of 1,3-dimethyl-6-azathymine **17** with 1-heptene. The reaction could also be extended to the irradiation of **17** with 2-heptene, cyclohexene, and 1-, 3-, or 4-methylcyclohexene to give **20** and **22**, respectively (87MI2). Photocycloaddition of dihalomaleimides **23** with **18** gave tricyclic **24** (83AG156) (Scheme 6).

Photochemical [2 + 2] cycloaddition of ketene and (trifluoromethyl)triazinone **25** gave **26** (88CPB3354). The role of the CF_3 group in the activation of the imine function of **25** was investigated (Scheme 7).

Azacyclobutane dimers **28** were obtained (84H67, 84H1363) in high yields by irradiation of some pyrimidine 6-azapyrimidine dinucleotide analogs **27**. They are unstable in aqueous solution and decomposed back to **27** (Scheme 8).



SCHEME 5

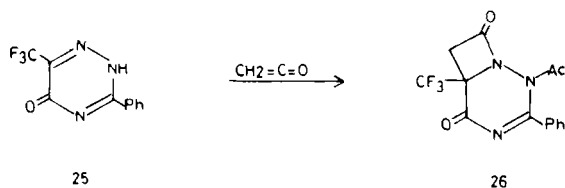


SCHEME 6

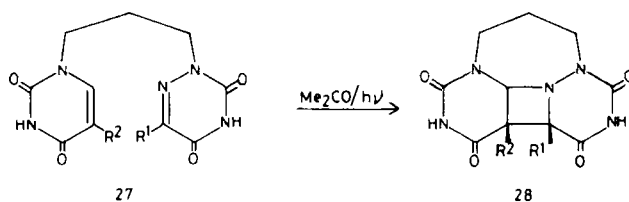
IV. Pyrrolo- and Indolo[1,2,4]triazines

A. PYRROLO[X,Y-Z]TRIAZINES

There are seven possible annulated [1,2,4]triazines with the pyrrole ring; one bicyclic system could be produced from each of the edges **b-f** of **1A** except that face **e** could form three bicyclic systems. All except those on face **e** incorporate one nitrogen of the triazine ring to form the annulated pyrrole ring and are characterized by the presence of that nitrogen as a bridgehead. Examples for pyrrolo[3,2-*e*]- and pyrrolo[3,4-*e*][1,2,4]triazines have not been reported during the period of our review.



SCHEME 7



SCHEME 8

1. *Pyrrolo*[1,2-*b*][1,2,4]triazines

Pyrrolo[1,2-*b*][1,2,4]triazinium salt **30** was obtained (90CB2039) by the reaction of hydrazone **29** with the Vilsmeier reagent prepared from DMF and oxalylchloride (Scheme 9).

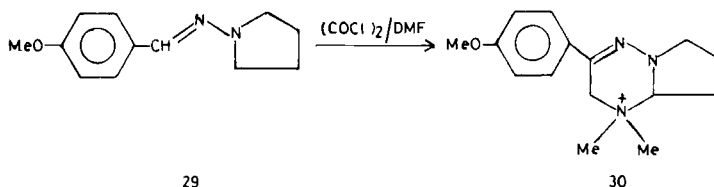
2. *Pyrrolo*[2,1-*c*][1,2,4]triazines

The pyrrolotriazines **32** were prepared from 3,4-dihydro-5-ethoxy-2*H*-pyrrole **31** by sequential reaction with hydrazine hydrate and α -oxoesters (85GEP3340026). They are useful as selective herbicides (Scheme 10).

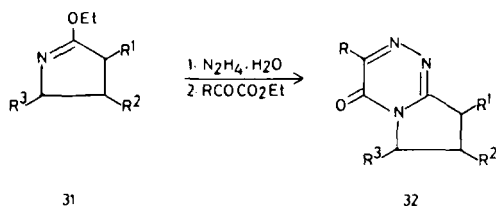
Dehydrogenation of the hydrazide derivative **33** with mercuric oxide in the presence of ethylene diamine tetraacetic acid (EDTA) gave **34** and **35** (77AP588). The latter (**35**) was prepared from a reaction of ester **36** with the appropriate lactam **37** (Scheme 11).

Cyclization of hydrazone **38** with mercuric oxide and EDTA gave dihydrotriazine **39** (87AP198). On the other hand, methyl hydrazone **38**, under 4-electron withdrawal and neighboring group participation reacts with the same reagent to give lactam **40**, a useful precursor for the synthesis of the pyrrolo[2,1-*c*]triazinium salt **41** by cyclization with perchloric acid (87AP258) (Scheme 12).

Pyrrolobenzotriazine **43** was obtained by reaction of **42** with nitrous acid. Its demethylation with boron tribromide gave **44**, whose oxidation



SCHEME 9

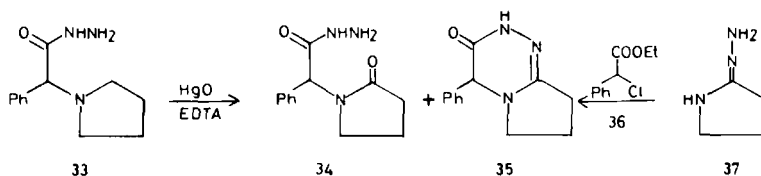


SCHEME 10

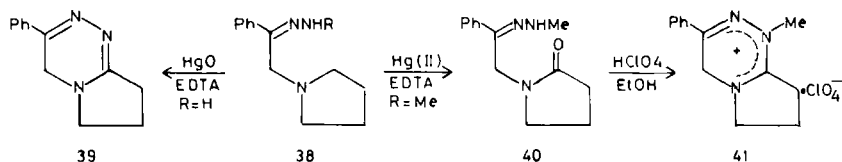
with silver oxide gave pyrrolo[2,1-*c*][1,2,4]benzotriazine-6,9-dione **45**. Diels-Alder reaction of **45** with cyclopentadiene gave **46** (80JHC1705) (Scheme 13).

3. Pyrrolo[1,2-*d*][1,2,4]triazines

The synthesis of 1,2-dihydro-1-oxopyrrolo[1,2-*d*][1,2,4]triazines **48** was achieved by rearrangement of 2-pyrrolyloxadiazoles **47** under alkaline conditions or by the cyclization of pyrrole-*N*-ethoxymethylidene hydrazides **52** either with alkali (80JHC631) or thermally (80JHC625). It was also obtained by the cyclization of **53** with triethyl orthoformate or triethyl orthoacetate (83MI3; 87MI5). Electrophilic substitution reactions of **48** were made either on the lactam nitrogen with dimethyl sulfate, benzyl chloride, and acetic anhydride or on the pyrrole ring with bromine and nitric acid. Hydrazine derivatives **50** were obtained (83MI3; 87MI5) by the conversion of **48** to the thioxo analogues **49** followed by reaction with hydrazine. Hydrazones **51** were prepared (87MI5) by reaction of **50** with appropriate aldehydes or ketones. Screening **48**, **50**, and **51** for antihypertensive activity in spontaneously hypertensive rats showed that the most active compounds were **48** (R = Me) and **51** (R = Me). The 1,4-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-*d*][1,2,4]triazines **55** were similarly prepared (81JHC743) by cyclization of **54** or by alkaline rearrangement of **56**. Methylation of **55** with dimethyl sulfate or diazomethane gave mixtures of *O*-methyl and *N*-methyl derivatives (Scheme 14).



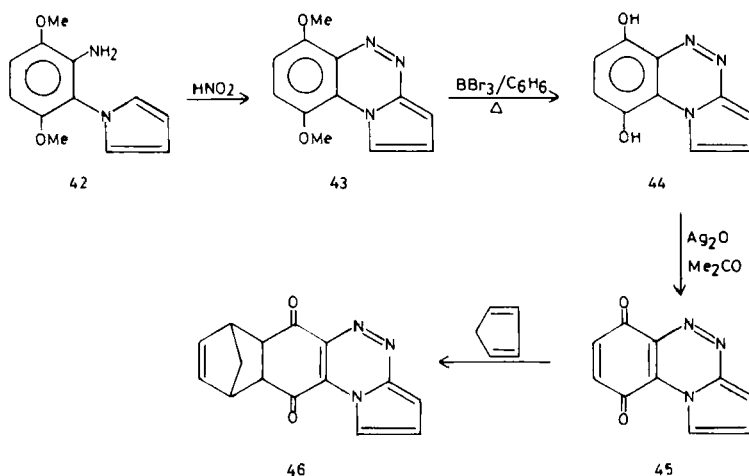
SCHEME 11



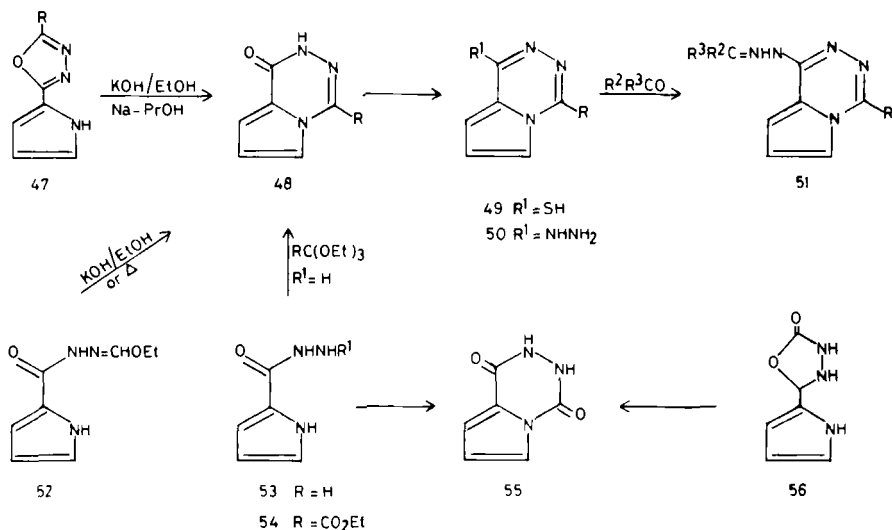
SCHEME 12

Cyclization of *N*-carbethoxyhydrazone **57** and *N*-formylhydrazone **58** of pyrrole-2-carbaldehyde gave **59** (73CC35; 80JHC631) by base-catalyzed cyclodehydration. The expected substitution product at 6-position was obtained from the reaction of **58** with *N*-bromosuccinimide (Scheme 15).

Annulated furo analogues of 1,2-dihydrofuro[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-1-ones **62** were obtained (84CCC65, 84MI4; 89MI3) by the cyclization of **61** with orthoesters. Compounds **61** were obtained by the reaction of **60** with hydrazine hydrate. Thioxo analogues **63** were prepared from **62** by reaction with phosphorus pentasulfide. Reaction of **63** with hydrazine gave **64**. A similar sequence of reactions was used for the synthesis of the benzo analogues **65** and **66** (84CCC65). The pentacyclic ring system, 1,2,4-triazino[4'',5'':1',5']pyrrolo[2',3':4,5]furo[3,2-*b*]indole **68**, was also prepared (86CZP230342; 87CZP232192) by the cyclization of hydrazide **67** with triethylorthoformate or triethylorthoacetate (Scheme 16).



SCHEME 13

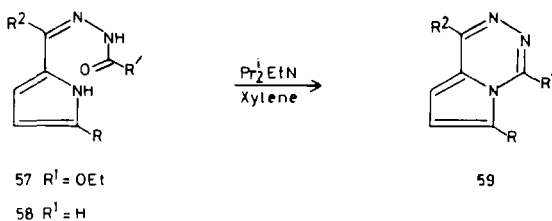


SCHEME 14

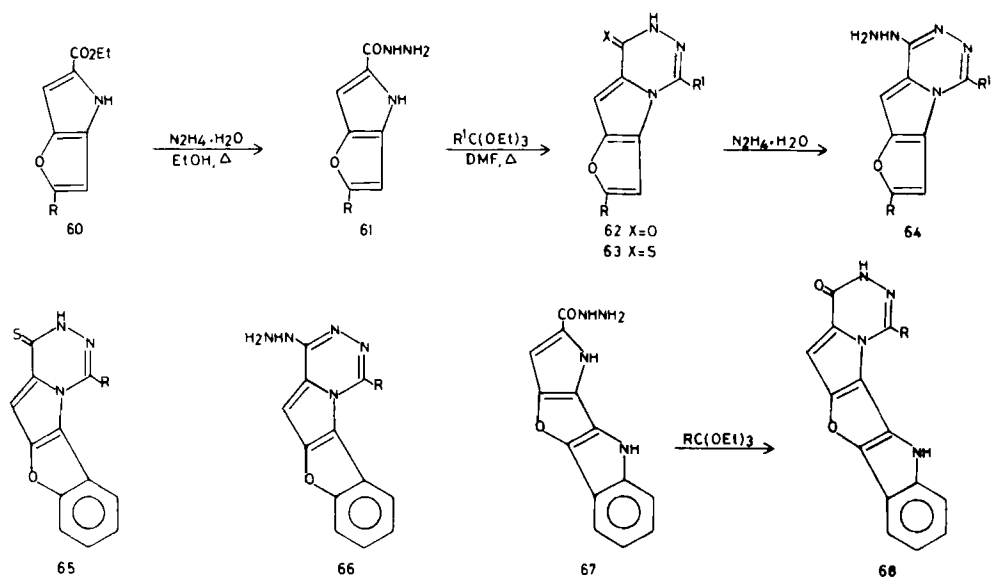
Cyclization of 8-hydrazino-3-phenyl-1-azaazulenes **69** with triethyl orthoformate gave 4,5-triazabenz[*cd*]azulene derivative **70** which was easily hydrolyzed on silica gel and gave (2-chloro-8-imino-3-phenyl-1-aza-1,8-dihydroazulen-1-yl) formaldehyde oxime (87H767) (Scheme 17).

The Mitsunobu reaction was applied to the synthesis of pyrrolo[1,2-*d*][1,2,4]triazines from pyrrole derivative **71**. Thus reduction of **71** gave alcohol **72**, which on treatment with diethylazodicarboxylate and triphenyl phosphine gave **74** via the open chain intermediate **73**. Hydrolysis of **74** gave **75** (84AG517) (Scheme 18).

Pyrrolo annulated triazine **77** was prepared (88TL4415) by the [6 + 4]-cycloaddition of azoniatulvene ion **76** with azomethine imines generated from benzylidene phenylhydrazone (Scheme 19).



SCHEME 15

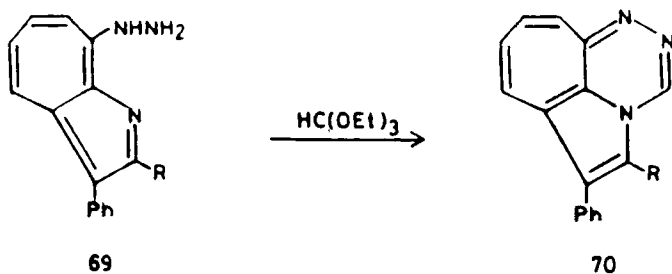


SCHEME 16

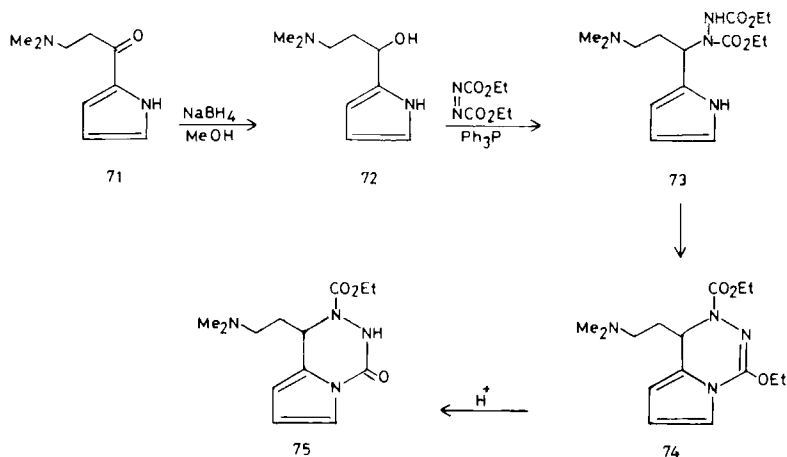
4. Pyrrolo[3,2-*e*][1,2,4]triazines

The synthesis of this ring system was achieved by the reaction of the ketene aminal **79** with 3-morpholino-1-ethyl-1,2,4-triazinium tetrafluoroborate **78** to give **80** (89IZV494). Cyclization of **78** with the bifunctional nucleophile **81** gave the pyrrolo[3,2-*e*][1,2,4]triazinones **82** (88TL1431). This reaction represents the first example of orthocyclization onto the 1,2,4-triazine ring by the addition of dienophiles at C-5,6 (Scheme 20).

Tricyclic **84** was prepared [91JCS(P1)1762] by the thermal intramolecular rearrangement of dichloro(pyrrolidinylcycloheptenyl)triazine **83**. Its structure was confirmed by X-ray crystallography (Scheme 21).



SCHEME 17

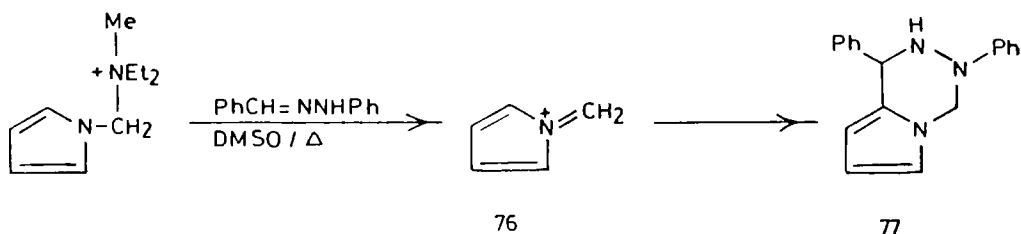


SCHEME 18

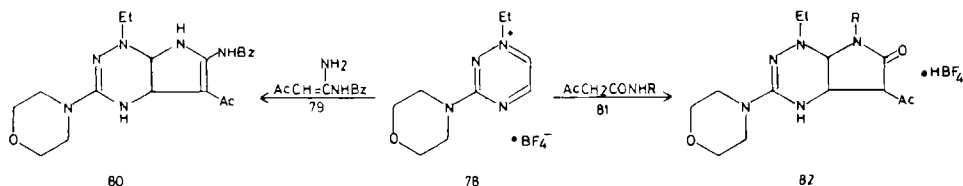
5. Pyrrolo[2,1-f][1,2,4]triazines

Cyclization of 1-ureidopyrroles **88** with a base gave (79JHC833) pyrrolo[2,1-f][1,2,4]triazines **89**. Pyrolysis of **89** ($\text{R}^2 = \text{COOH}$) afforded **90**. Compounds **88** were prepared by treating chloroacetone semicarbazone **85** with the sodium salts of diethyl oxalacetate or oxalylacetophenone **86** to give semicarbazones **87**, which were converted to **88** by the action of hydrochloric acid (Scheme 22).

Treatment of 1,2,4-triazines **91a–91e** with the electron-deficient dienophile dimethyl acetylenedicarboxylate gave products, depending on the substituents [77LA(10)1718]. Pyrrolo-[2,1-f][1,2,4]triazines **92** were obtained via [4 + 2]-cycloaddition [77LA(9)1413, 77LA(10)1718] with **91**, but interaction with **91b** in the absence of solvent gave, in addition to **92**, the pyrido[2,1-f][1,2,4]triazine **93** and [1,3]oxazino[2,3-f][1,2,4]-triazine **94**. In case of **91a** pyridine and benzene derivatives were also formed in addition to **92** (Scheme 23).



SCHEME 19



SCHEME 20

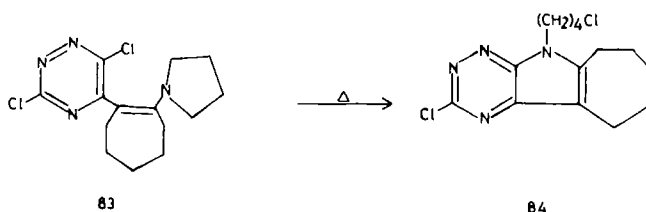
B. [1,2,4]TRIAZINO[X,Y-Z]INDOLES

The skeleton of the triazino-indoles and isoindoles may be derived from the pyrrolotriazines by fusion of a benzenoid ring onto the pyrrole. Pyrrolo-triazines with bridgehead nitrogen may result from both indole and isoindole rings, whereas those whose fusion are [2,3-*e*] and [3,2-*e*] provide only indole analogues and those with [3,4-*e*] do not allow the fusion of the benzo ring. This means that there are six possible indole- and four isoindole-fusion derivatives. It should be noted that face *z* belongs to the indole or isoindole ring and not to the triazine ring as in pyrrolotriazines.

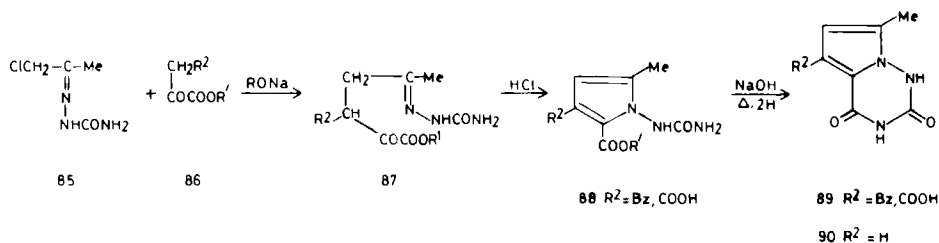
1. [1,2,4]Triazino[1,6-*a*]indoles

Treatment of 1-ethylideneamino-3-methylindole **95** with *p*-toluene sulfonic acid in boiling benzene gave 1,2-dihydro[1,2,4]triazino[1,6-*a*]indole **96** (75CPB2891). The reaction was said to be due to an initial formation of a Diels–Alder-type adduct followed by the liberation of 3-methylindole. Compound **96** was oxidized either on exposure to air or by the action of chloranil to give **97** (Scheme 24).

Azomalonates carrying an electrophilic side chain, as in **100** and **101**, could be cyclized to give the title ring system. They were prepared by coupling of dimethyl 2-(2-chloro-*N*-methyl or phenylacetamido)malonate



SCHEME 21

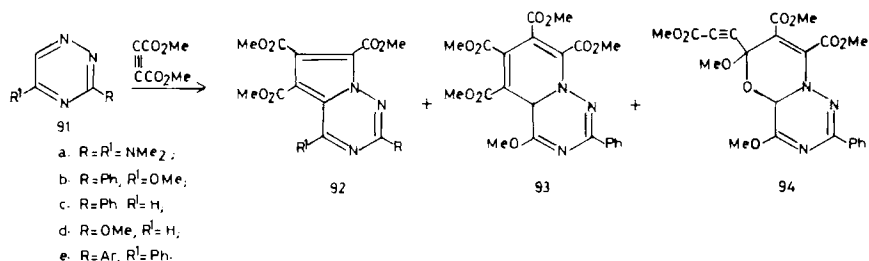


SCHEME 22

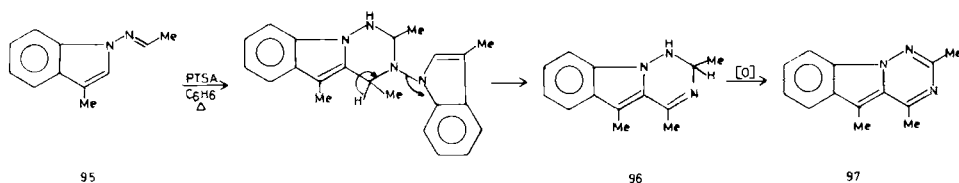
with diazotized 2-amino-5-chlorobenzophenone (**98**) or methyl antranilate **99**. Reaction of **100** with two equivalents of sodium methoxide gave the triazino[1,6-*a*]indoles **102** (90HCA1700). Alternatively, triazines **104** were isolated when only one equivalent of sodium methoxide was used. Further aldol-type condensation took place with another equivalent of base to give **102** (90HCA1700). On the other hand, triazino[1,6-*a*]indoles **103** could not be prepared in acceptable yield by the action of base on **101**. Ring closure to **103** was achieved (90HCA1700) in moderate yield by heating **105** in dimethylformamide dimethyl acetal (90HCA1700) (Scheme 25).

2. [1,2,4]Triazino[4,5-*a*]indoles

1,2-Dihydro-1-oxo[1,2,4]triazino[4,5-*a*]indoles **108** were prepared (80JHC77; 87JMC1029; 88M12; 89JPS780; 84M15) by boiling **106** with orthoesters or by thermal cyclodehydration of **107**. Reaction of **108** with phosphorus pentasulfide gave **109** (79JHC1193; 80JHC77), whose reactions gave **111** and triazinoindole derivatives **112** (79JHC1193). Reaction of **108** with phosphorus oxychloride gave chloro derivatives **110**, which then gave **111** with hydrazine (80JHC77). Compounds **108** and **111** were



SCHEME 23



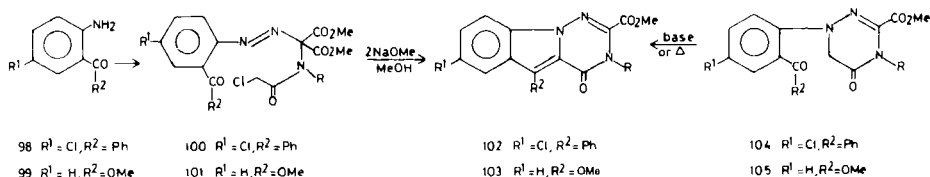
SCHEME 24

tested for antihypertensive activity in rats and toxicity in mice; some are more active than hydralazine, but all are much less toxic (83MI4). Hydrazine **111** and its derivatives were tested for blood platelet aggregation inhibition, antihypertensive activity, and thromboxane synthetase inhibition (87JMC1029; 88MI2) (Scheme 26).

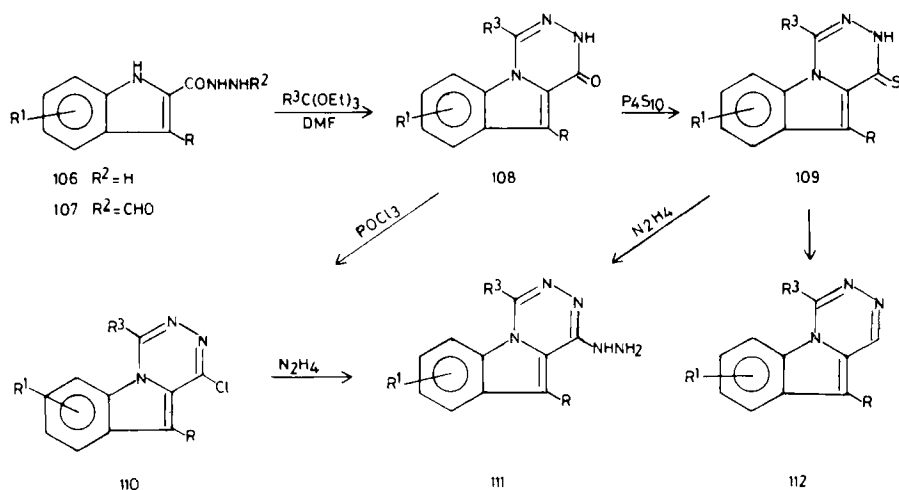
Derivatives such as **114** were prepared by rearranging oxadiazolylin-doles **113** with potassium hydroxide. They were also obtained (77JHC1365) by cyclizing indole-*N*-ethoxymethylidene hydrazide **115**. Triazinoindolones **114** underwent electrophilic substitution on the lactam nitrogen by dimethyl sulfate or benzyl chloride and on the benzene ring by bromine or nitric acid. The latter reagent gave a mixture of polysubstituted derivatives with the first substitution occurring at the 10-position (78JHC1209). Some 10-methyl-1,2-dihydro-1-oxo[1,2,4]triazino[4,5-*a*]indoles possess fairly potent antimicrobial activity (89JPS780) (Scheme 27).

Condensation of **116** with ethyl chloroformate afforded **117**, which on cyclodehydration with ethanolic potassium hydroxide (79JHC1217) or with phosphorus oxychloride [88IJC(B)1102] gave 1,2,3,4-tetrahydro-[1,2,4]triazino[4,5-*a*]indole-1,4-dione **119**. The latter was also prepared (79JHC1217) by rearranging **118**. Methylation of **119** with dimethyl sulfate gave a 9 : 1 mixture of **120** and **121**, whereas with diazomethane it afforded a mixture of **122** and **123** [75CR(C)521]. The methylation was reinvestigated (79JHC1217) (Scheme 28).

The reaction of 1-acetyl-3-indolinone **124** with carbon disulfide in the presence of sodium hydride gave thiazolo[3,4-*a*]indolium ion **125**. Reaction of **125** with hydrazine or phenylhydrazine gave 2*H*[1,2,4]triazino[4,5-*a*]indole **126** (75YZ980) (Scheme 29).



SCHEME 25

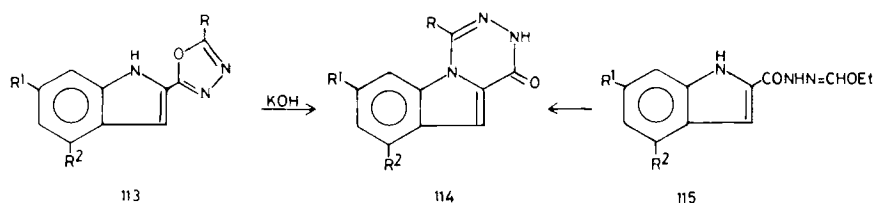


SCHEME 26

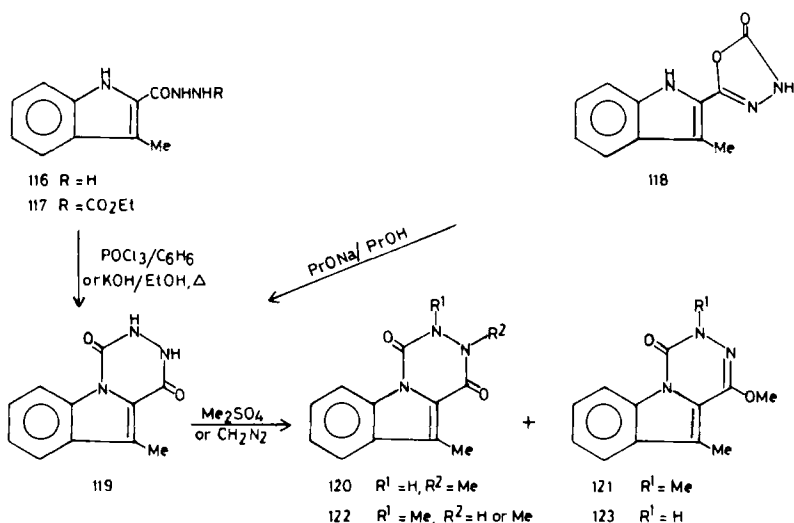
The Mitsunobu reaction was also applied to the synthesis of [1,2,4]triazino[4,5-*a*]indoles (84AG517). Thus, reaction of the 2-acylindoles **127** with sodium borohydride in methanol or with lithium aluminium hydride in tetrahydrofuran gave the corresponding alcohols **128**. Their cyclization with diethyl azodicarboxylate in the presence of triphenyl-phosphine gave the triazinoindoles **129**. Acid treatment of the latter afforded **130** (Scheme 30).

3. [1,2,4]Triazino[5,6-*b*]indoles

Much work is still appearing on the [1,2,4]triazino[5,6-*b*]indole ring system since its first synthesis, due to its varied biological properties. Moreover, it has been used as a carrier for diverse functional groups suitable for the development of several chemotherapeutic agents. In addi-



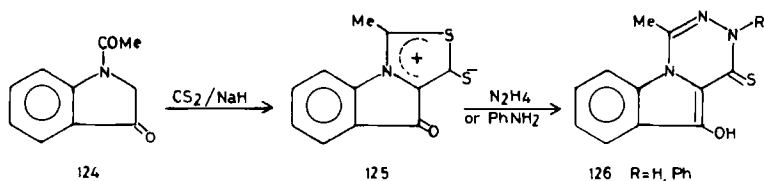
SCHEME 27



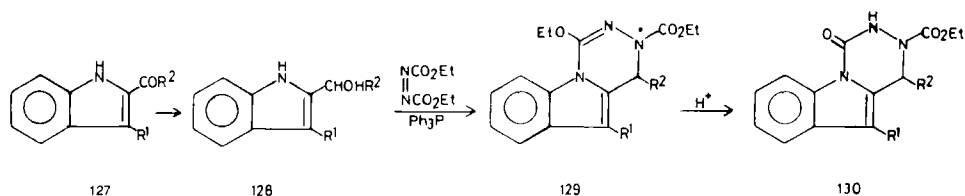
SCHEME 28

tion to the previously mentioned review (78HC749), a second on 1,2,4-triazinoindoles has been reported (78H1631). The general method for its synthesis involved the condensation of isatin with thiosemicarbazide to afford **131**, which cyclized to [1,2,4]triazino[5,6-*b*]indole-3-(2*H*,5*H*) thione **133** in alkaline medium. Semicarbazone **132** did not cyclize to the [1,2,4]triazinoindole **134** but instead gave 6-(2-aminophenyl)-1,2,4-triazine-3,5-(2*H*,4*H*)dione **138**. Ring closure of **138** could be effected in an acid medium or in boiling *N,N*-dimethylformamide. The same procedure was used for the synthesis of the 8-methyl (82MI2), 6,7-dimethyl (80H1139), 5-fluoro, 6-fluoro, and 4-trifluoromethyl (80JPR314) derivatives of **133**.

It has been said that the above procedure cannot be applied to the synthesis of the corresponding nitro derivative, 8-nitro[1,2,4]triazino[5,6-*b*]indole-3-thione. Thus, heating 5-nitroisatin-3-thiosemicarbazone in aqueous potassium carbonate gave after acidification a mixture of oxotriazinethione **137** and 5-nitroindazole 3-carboxylic acid (90ZOR1327).



SCHEME 29



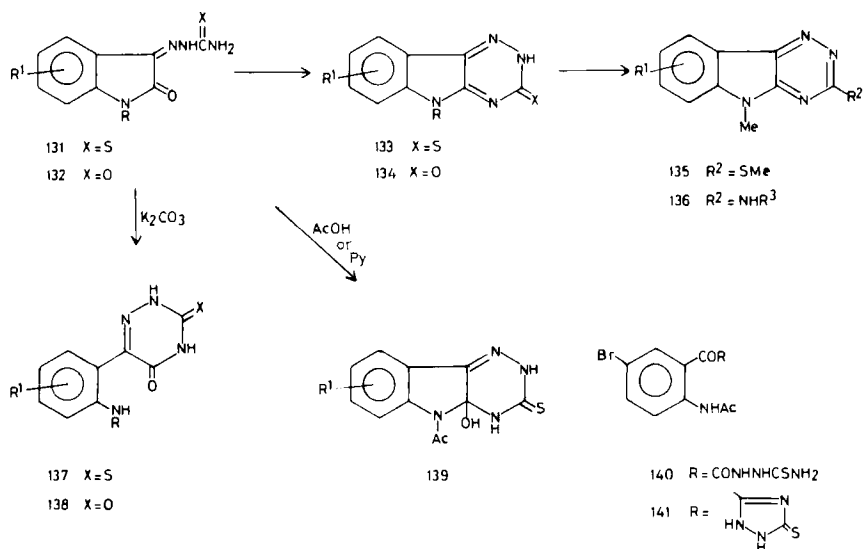
SCHEME 30

The cyclization of 1-methylisatin-3-thiosemicarbazone to **133** ($R = \text{Me}$) has been reported (75JHC1001). S-methylation of **133** followed by displacement of the methylthio group of **135** by the appropriate amino alcohol yielded **136**. The effect of the methyl group on the cyclization of **131** has been studied (74ZOR1962). Energies of activation for cyclization of **131** with methyl substituents were determined. The effect of acidity on the rate constants associated with closing of the triazine ring in isatin 3-thiosemicarbazone and its methyl derivatives has been studied (78ZOR1544).

5-Acetyl-4,4*a*-dihydro-4*a*-hydroxy[1,2,4]triazino[5,6-*b*]indole-3(2*H*)thione **139** was found (81ZOR589) to be the product obtained by reacting 1-acetylisatin with thiosemicarbazide in acetic acid or pyridine. Cyclization occurred readily but it is difficult to isolate the respective thiosemicarbazone in a pure form. The latter is formed during condensation in glacial acetic acid at room temperature and is converted fully into the ring isomer. On the other hand, condensation of 1-acetyl-5-bromoisatin with thiosemicarbazide showed certain peculiarities caused by the introduction of the bromine atom into the indole ring. When the reaction was carried out in ethanol, **131** was formed, whereas in acetic acid solvent (90ZOR860) thiosemicarbazide derivative **140** was prepared. Ring closure of **131** ($R = \text{Ac}$) with alkali gave **133** ($R = \text{H}$), whereas **140** with alkali gave either triazole **141** or triazine **137** ($R = \text{Ac}$), depending on the concentration of alkali (Scheme 31).

Triazinoindole **146** was obtained (74T3997) in a mixture with quinoline **148** on thermolysis or of 3-(alkylthio)-6,7-dihydro[1,2,4]triazino[1,6-*c*]quinazolin-5-ium-1-olate **144** acid hydrolysis. The reaction presumably took place via the decomposition of **144** to a ketone and **142**, which then cyclized. Compound **144** was prepared by the condensation of **142** with aldehydes, ketones, or their equivalents. Reaction of **142** with 3-amino propanol gave **143**, which cyclized to **145** and then to **147** with base [80ACH(104)107] (Scheme 32).

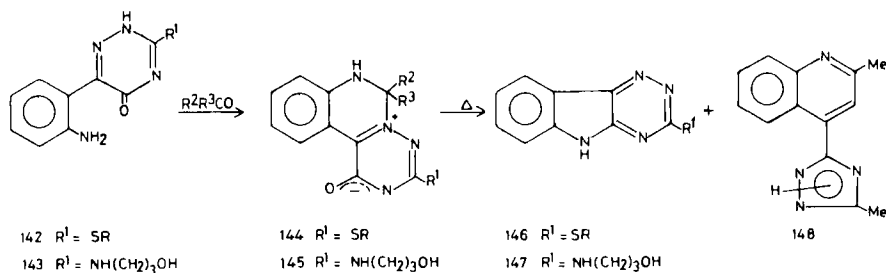
The synthesis of 2-aryl-2,3-dihydro[1,2,4]triazino[5,6-*b*]indol-3-ones **151** has been carried out (80MI2) by the cyclization of arylazoindolyl



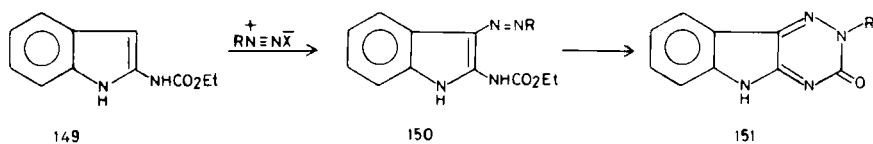
SCHEME 31

carbamate **150** that was prepared by treatment of ethyl-2-indolyl carbamate **149** with aryl diazonium salts (Scheme 33).

Methylation of the 6,7-dimethyl derivative of **133** with methyl iodide in sodium hydroxide or sodium ethoxide gave two *S,N*-dimethyl derivatives, whereas in sodamide or ammonia, only the *S*-methyl derivative was obtained. Methylation with diazomethane gave four methyl derivatives and with methyl chloride two di-*N*-methyl and one *S,N*-dimethyl derivative were obtained (80H1139). Methylation of **153**, obtained from **152**, gave 4-methyl-3-methylthio-triazinoindole **155**, whose hydrolysis or oxidation gave **154** (76T1735). On the other hand, methylation of **156** gave methiodide



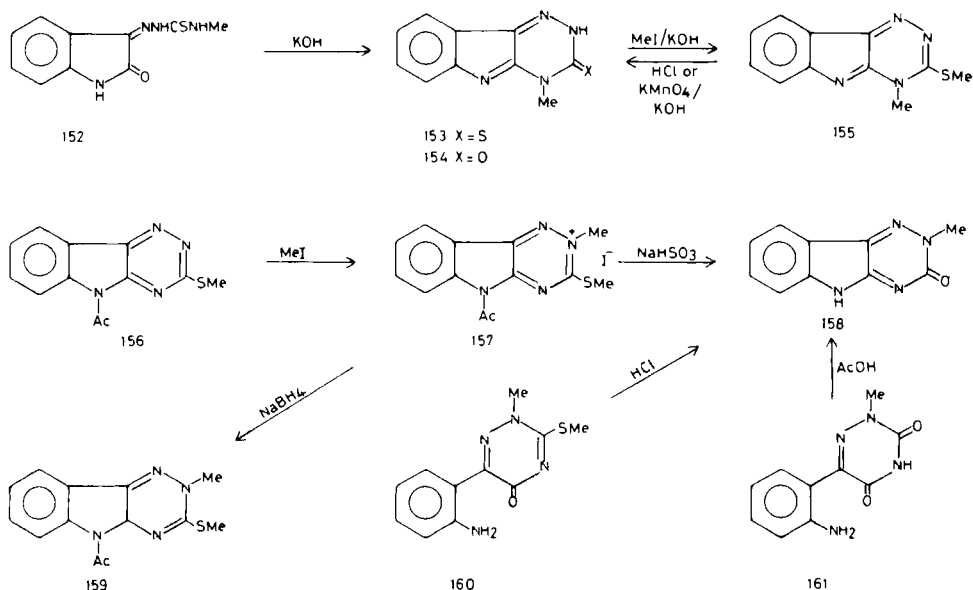
SCHEME 32



SCHEME 33

157, whose reduction gave **159**. Hydrolysis of **157** furnished **158** (76T1735). The latter was also obtained from **160** or **161** (Scheme 34).

Various 3-amino derivatives of that ring system, such as amines, hydroxylalkylamines, a morpholine, a piperidine, or substituted hydrazines, were prepared and tested as new blood platelet aggregation inhibitors with antihypertensive action [72JMC277; 80ACH(104)107; 87MI6; 91MI3]. 3-Dialkylaminoethylthio-5H[1,2,4]triazino[5,6-*b*]indoles **163** were prepared by the reaction of sodium salt **162** with dialkylamino ethyl chloride hydrochloride (80JPR314). Compounds **133** and **163** showed no activity as depressants or analgesics. The corresponding morpholino derivatives of **163** were screened for bactericidal, fungicidal, and virucidal activity (80JIC1176). Triazinoindoles **133** are novel herbicidal compounds that provided complete control of a large number of weed species as well



SCHEME 34

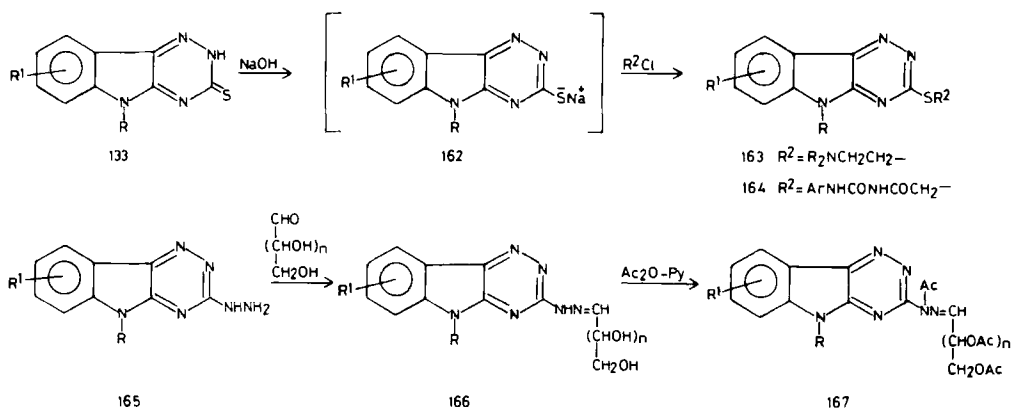
as selective weed control in wheat [87ABC3177, 87JAP(K)62/132882]. Electron impact fragmentation of **133** has been reported (90MI1).

Indolotriazinylthioacetyl ureas **164** were prepared (85JIC165) by treating **133** with chloroacetyl ureas. All were screened against *S. aureus* bacteria and *Sunnhemp rosette* virus; some markedly inhibited both bacterial and viral growth. Reaction of **133** with ethyl chloroacetate gave derivatives of great value for the synthesis of heterocyclic compounds (93AP153).

Reaction of thione **133** or its alkylated derivative with hydrazine gave (72JMC277) 3-hydrazino[1,2,4]triazino[5,6-*b*]indole **165**, which is an excellent precursor for the synthesis of heterocyclic compounds. Its hydrazones were prepared (82MI6) by the condensation of acetophenones with fluoro derivatives of **165**; they are useful bactericides. The reaction of hydrazines with 5-nitrofurfural diacetate gave the respective hydrazones, which exhibited bactericidal activity (88JIC524). The pyridine aldehyde derivative had antitumor activity against P388 lymphocytic leukemia in mice (87PHA664).

Reaction of hydrazine **165** with a number of monosaccharides give hydrazones **166** (92BCJ546). Their acetylations gave peracetyl derivatives **167**. The same reactions were extended to the *N*-methyl and the 7-methyl derivatives of **165** (93JPROO). That compounds **166** exist as open-chain structures was based on a 2D NMR study (93MI1) (Scheme 35).

Condensation of **165** with chloroacetamide derivatives afforded (89JIC246) carbamoylhydrazino derivatives **168**. Some are active against *S. aureus* and *Escherichia coli*. Condensation of **165** with ethyl cyanoacetate, malononitrile, ethyl acetoacetate, or acetylacetone gave (87AP1191, 87PHA664; 89JHC769) **169** and **170**, whose bactericidal activity has been reported.

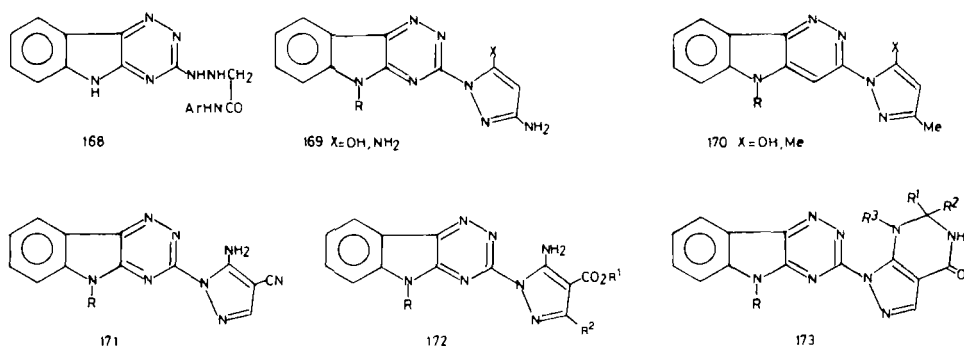


SCHEME 35

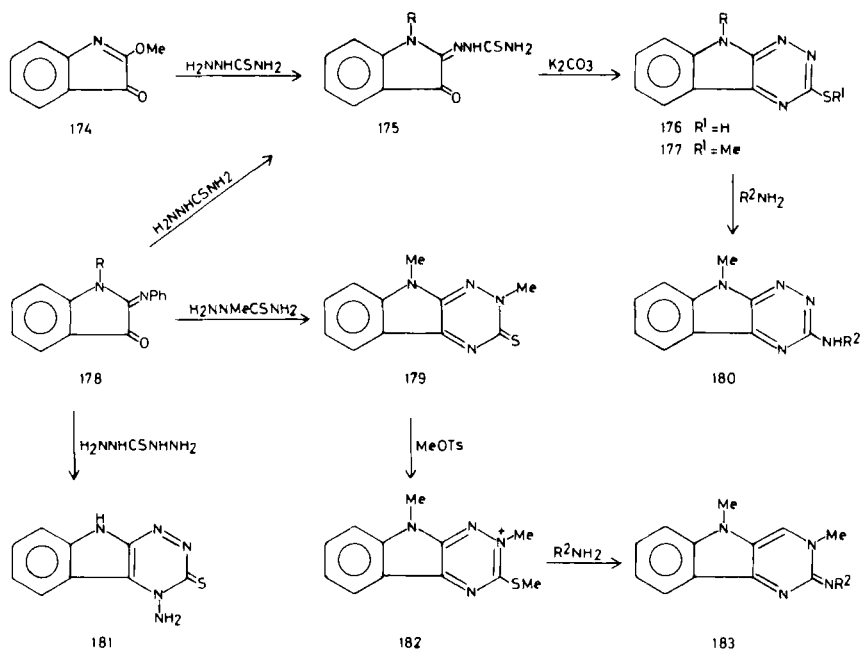
Condensation of **165** with ethoxymethylenemalononitrile gave **171**, and with ethyl ethoxymethylenecyanoacetate or methyl bis(methylmercapto)-methylene cyanoacetate it yielded **172** (80AP108). The reaction of **172** with urea, thiourea, and benzyl nitrile afforded **173** (91PHA98). Treatment of hydrazino derivatives **165** with alkyl, aryl, or aralkyl isothiocyanates yielded (86JHC1731) 3-(*N*-substituted-thiocarbamoyl)-hydrazino[1,2,4]triazino[5,6-*b*]indoles which have been evaluated for *in vitro* antimicrobial activity (Scheme 36).

4. [1,2,4]Triazino[6,5-*b*]indoles

The first synthesis of [1,2,4]triazino[6,5-*b*]indole (78H1631) was reported by Russian workers (71ZOR179). They reacted isatin-2-anil **178** with thiosemicarbazide to give isatin-2-thiosemicarbazone **175**, which also could be cyclized to the triazinoindole **176** by aqueous potassium carbonate. Reaction of **178** with methylthiosemicarbazide gave **179** (74JOU103; 75JHC1001). The reaction of **178** with excess 3-thiocarbazide afforded 4-amino derivative **181**. Alkylation of **177** or **179** with methyl tosylate gave **182**. Reaction of amines with **177** and **182** gave **180** and **183**, respectively. The oxygen analogues of the compounds in Scheme 37 were also prepared (75JHC1001). Compounds **180** and **183** were tested *in vitro* against Rhino 2 virus. A large number of compounds, including 2- and 3-thioacylhydrazones of isatin and their cyclized derivatives, were tested for toxicity and anti-inflammatory activity in mice and rats. The most active anti-inflammatory agents were compounds **181** (86KFZ1051). Structure-activity relationships were also studied (86KFZ1051). The most active compounds were those lacking substituents on the indole nitrogen atom. Introduction of alkylthio groups decreased activity.

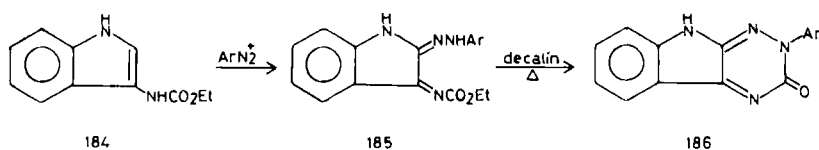


SCHEME 36



SCHEME 37

A synthetic approach to this heterocycle was reported by diazotization and coupling of a substituted aniline or naphthylamine with 3-(ethoxycarbonylamino)indole **184** to afford hydrazone **185**, which was subsequently cyclized (75MI4) to **186** in boiling decalin. A similar approach was also reported (78CCC960; 80MI2), but the diazotization of **184** was carried out in pyridine, whereby the respective arylazoindolyl carbamates were obtained. Thermal cyclization of the latter also gave the desired ring system **186** (Scheme 38).



SCHEME 38

C. [1,2,4]TRIAZINO[x,y-z]ISOINDOLES AND
[1,2,4]TRIAZINO[3,4-a]ISOINDOLES

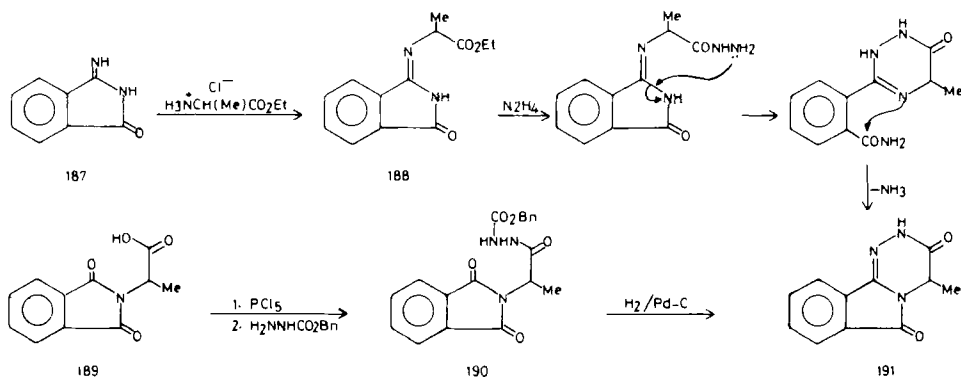
Treatment of *N*-(3-oxo-1-isoindolinylyden)alanine ethyl ester **188**, obtained by the reaction of 3-iminoisoindolin-1-one **187** with alanine ethyl ester, with hydrazine hydrate gave (80HCA1797) 4-methyl-2,3,4,6-tetrahydro[1,2,4]triazino[3,4-*a*]isoindole-3,6-dione **191** instead of the previously postulated 6-hydroxy-2-methyl-2,3-dihydro[2,1-*a*]phthalazin-3-one. The reaction mechanism is shown in Scheme 39 and its structure has been established by X-ray analysis. An independent synthesis starts from 2-phthalimidopropionic acid **189** and phosphorus pentachloride, followed by reaction with benzyloxycarbonylhydrazine to give the phthalimido-propionohydrazide **190**, which underwent hydrogenolysis in the presence of Pd-C to give **191**.

The reaction of isoindole **192** with phosphorus pentasulfide in pyridine afforded intermediate **193**, which gave with hydrazine hydrate **194** (82S853) (Scheme 40).

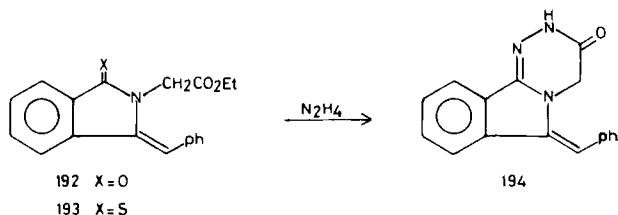
V. Furo[1,2,4]triazines

FURO[x,y-z][1,2,4]TRIAZINES

Fusion of a heterocycle having an oxygen or sulfur atom onto the triazine ring could occur only at its face *e*, otherwise it will be categorized as a heterocycle with more than one heteroatom. Three combinations are possible for that type of fusion. However, only two of them were reported during the period covered by the review.



SCHEME 39



SCHEME 40

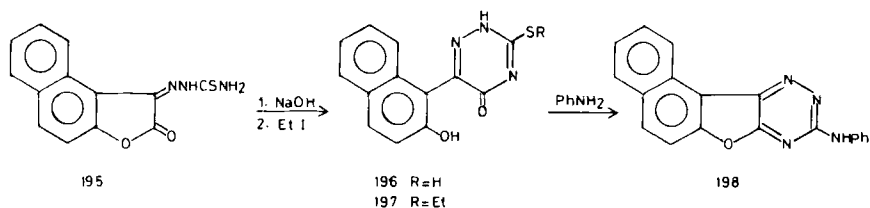
1. *Furo*[2,3-*e*][1,2,4]triazines

Naphtho[2,1-*b*]furo[2,3-*e*][1,2,4]triazines **198** were prepared (88JHC-1117) by the reaction of 4-5-benzocoumaran-2,3-dione with thiosemicarbazide to give **195**, whose ethylation in the presence of sodium hydroxide gave **197** via **196**. Reaction of **197** with aniline gave **198** via the first displacement of the ethylthio group whose product could be isolated with a shorter reaction time. On the other hand, the similar sequence of reactions on coumaran-2,3-diones differs markedly from that of 4,5-benzocoumaran-2,3-diones, where the cyclization of **195** to **198** could not be effected. The behavior of the later dione resembles that of isatin and thianaphthenequinone (Scheme 41).

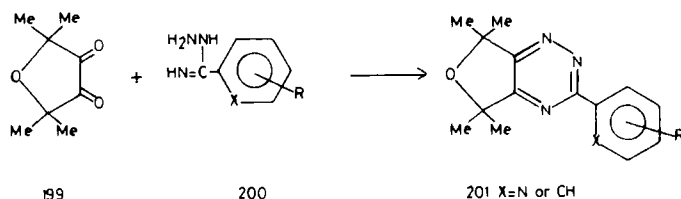
2. *Furo*[3,4-*e*][1,2,4]triazines

Furo[3,4-*e*][1,2,4]triazines **201** were prepared (75USP3962240; 77USP-4013767) by condensing furandione **199** with the respective 2-aryl or pyridylcarboximide acid hydrazide **200**. Compound **201** (X = N) was oxidized to its *N*-oxide. Both **200** and **201** have sedative and tranquilizer properties (Scheme 42).

Furo[3,4-*e*][1,2,4]triazine 4-oxides **203** were prepared (75GEP2517994; 76USP3963713; 79JHC1389) from furandione-3-hydrazone-4-oxime **202**



SCHEME 41



SCHEME 42

and triethyl orthobenzoates. Reduction of **203** gave **204**. A number of ^{13}C -NMR spectra were studied (79JHC1389) and correlated with model compounds. The chemical shifts of the carbons of para-substituted 3-phenyl[1,2,4]triazine-4-oxides were studied using Swain–Lupton F and R values. Substituent chemical shifts in the triazines behaved in a manner similar to that in biphenyls. The central nervous system sedative–hypnotic activity of 3-arylfuro[3,4-*e*][1,2,4]triazine 4-oxides was measured. The *p*-nitro derivative emerged as a potent sedative hypnotic with unique pharmacological properties (81JMC490) (Scheme 43).

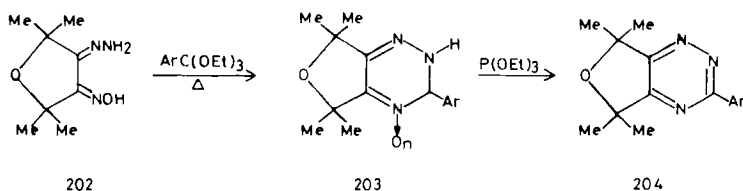
Cyclocondensation of 3,4-dihydroxy-2,5-furandicarboxylate dimethyl ester **205** with acetohydrazidehydrazone hydrochloride **206** gave **207** (89LA105) (Scheme 44).

VI. Thieno[1,2,4]triazines

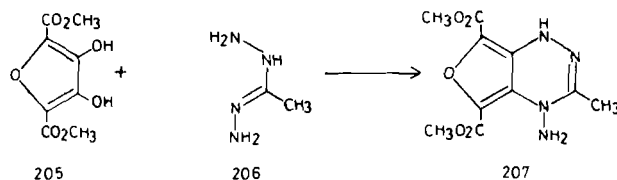
THIENO[x,y-z][1,2,4]TRIAZINES

1. Thieno[2,3-*e*][1,2,4]triazines

Thienotriazines **209** were prepared by cyclization of 5-oxo[1,2,4]triazines of type **208** or **210** by reaction [78CI(L)585; 83JHC1709; 88M11; 90M13] with phosphorus pentasulfide in pyridine. Analogously, 2-methyl-



SCHEME 43



SCHEME 44

3-mercapto-5-oxo-6-vinyl-2,5-dihydro[1,2,4]triazines were readily converted into the corresponding thieno[2,3-*e*][1,2,4]triazine (82JHC913), but 4-methyl-3-mercapto-5-oxo-6-vinyl-4,5-dihydro[1,2,4]triazine is only converted into the 5-thioxo analogue. The mechanism of the cyclization was reported. Derivative **209** was prepared [78CI(L)585] by reaction of **209** (R = SME) with morpholine (Scheme 45).

2. Thieno[3,4-*e*][1,2,4]triazines

Thieno[3,4-*e*][1,2,4]triazine **212** was prepared by cyclizing **211** with acetohydrazide-hydrazone hydrochloride (89LA105) (Scheme 46).

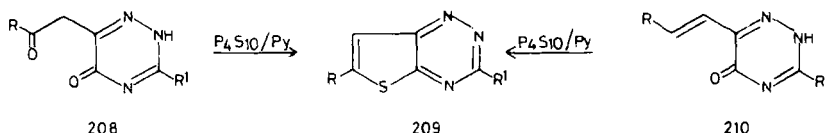
VII. Diazolo[1,2,4]triazines

A. [1,2]DIAZOLO[x,y-z][1,2,4]TRIAZINES

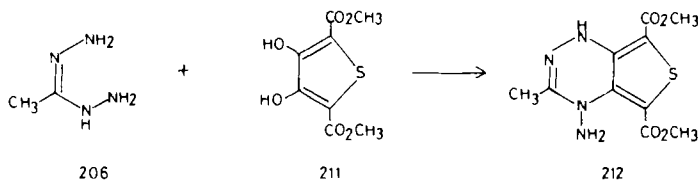
There are seven isomeric bicyclic rings of this class. Five have a bridge head nitrogen. Examples of all have been reported. A survey of this ring system has been included in a review [90AHC(48)223].

1. Pyrazolo[1,2-*a*][1,2,4]triazines

This type of ring system appears as salt **215**. Thus, the reaction of azauracils **213** with dibromopropane at 78–85°C gave bromopropyl derivatives **214**, whereas at 110–120°C the cyclized salts **215** were formed (82MI7, 82MI8) (Scheme 47).



SCHEME 45



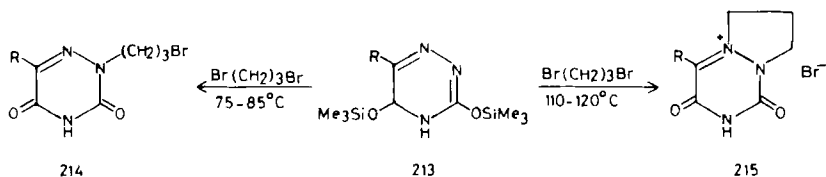
SCHEME 46

Other examples of this ring system are benzo analogues **217**, which were prepared [75JAP(K)75/140495] by ring closure of **216** using phosphorus oxychloride. They were prepared as analgesic and anti-inflammatory agents [75JAP(K)75/140495]. The synergistic effect of azapropazone **218** on the enzyme activities in an experimental granuloma was studied (76MI2). It is a nonsteroidal anti-inflammatory drug that increased capillary resistance in rats (82MI1) and displaced warfarin from its human plasma albumin binding (78E1320). Its binding to human serum albumin (80MI3) and its effect on formalin arthritis potentiated by prostaglandins (76MI4) were studied. Xanthine oxidase inhibitors containing **218** or its analogues were used for the treatment of uric acid diathesis (81EUP28660). The disposition of **218** in chronic renal and hepatic failure (81MI1) and its effect on gastrointestinal tract and liver (77MI2) as well as its pharmacokinetics following single oral and intravenous doses were studied (79AF971; 83MI5). Chromatographic analysis and determination in urine by direct quantitative thin-layer chromatography and HPLC (77MI1; 78AF1430; 83AF504) were investigated. Its toxicity was also studied (76MI1) (Scheme 48).

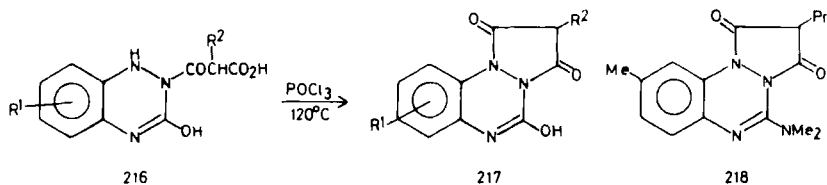
Cyclization of pyrazole **220** ($R = NH_2$), obtained from the reaction of 2-nitophenylhydrazine with **219** and subsequent hydrogenation, gave (81USP4260751) pyrazolo[1,2-*a*][1,2,4]benzotriazines **221**, a useful anti-inflammatory agent (Scheme 49).

2. Pyrazolo[1,5-*b*][1,2,4]triazines

The first synthesis of this heterocyclic ring system, **224**, was carried out (86S71) by the amination of aminopyrazole **222** with H_2NOSO_3H fol-



SCHEME 47

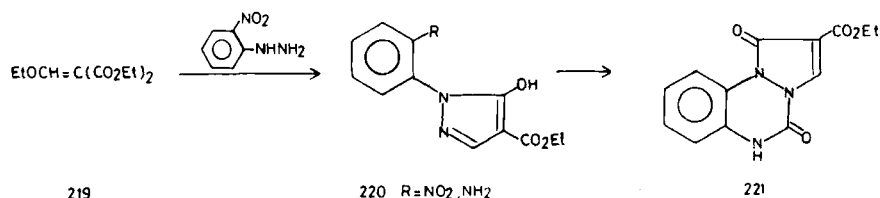


SCHEME 48

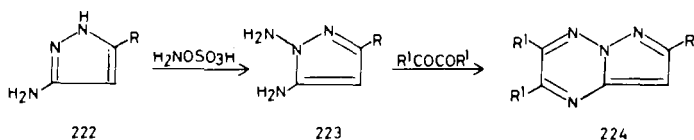
lowed by cyclocondensation of the resultant 1,5-diaminopyrazole **223** with diketones. The spectra of the parent heterocycle and the X-ray diffraction of its 2,3-dimethyl derivative have been reported (89JHC1109) (Scheme 50).

3. *Pyrazolo[5,1-c][1,2,4]triazines*

Regiospecific 1,7-cycloaddition reactions of 3-diazopyrazoles with electron-rich olefins and acetylenes have been reported [77JA633, 77S556; 78CB2258; 81TL1199; 83JOC2330; 87JOC5538; 90JCS(P2)1943] to be an effective method for the synthesis of pyrazolotriazines. They were believed to occur by a thermally allowed ($4n + 2$ electron) 1,7-cyclic process and/or by an allowed ($4n + 2$ electron) 1,3-cyclisation followed by [1,5]sigmatropic rearrangements and/or ring opening and reorganization. The isolation and detection of two sequentially formed intermediates, spiro-3*H*-pyrazole **229** and **231**, in the reaction of 1,1-dimethoxyethylene with **225** (87JOC5538) indicated that a 1,3-dipolar addition had occurred first to give **229**, which isomerized to **230**, and then to presumed intermediate **231**, which eliminated methanol to give pyrazolo[5,1-*c*][1,2,4]triazine **226**. The reaction of 3-diazo-5-phenyl-3*H*-pyrazole with 1,1-dimethoxyethylene gave 1,4-dihydro-4,4-dimethoxy-7-phenylpyrazolo[5,1-*c*][1,2,4]triazine, which eliminated methanol [90JCS(P2)1943]. This is inconsistent with a 1,7-cycloaddition as an initial step and another mechanism was



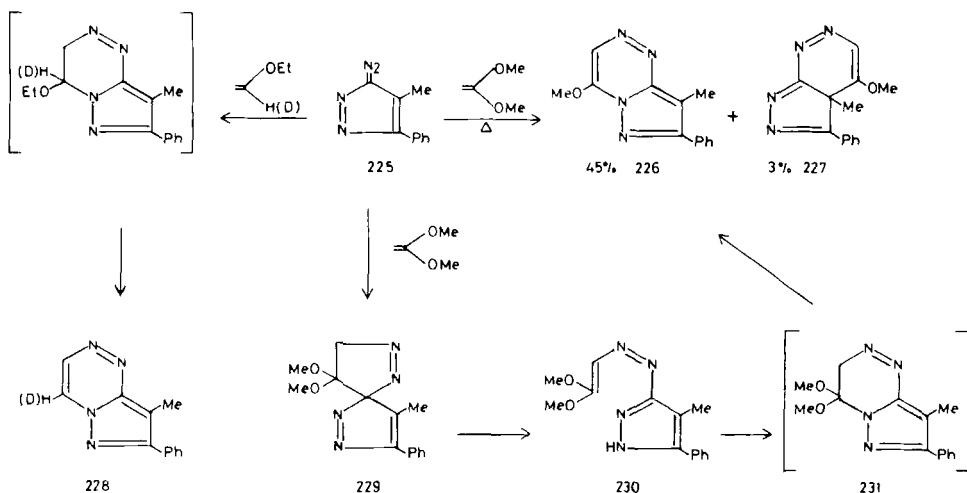
SCHEME 49



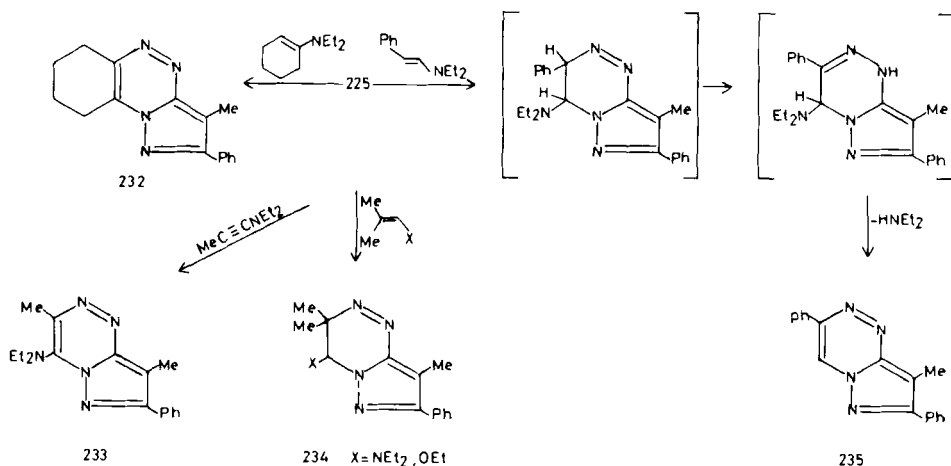
SCHEME 50

advanced to account for the formation of the products. It involves an initial 1,3-dipolar cycloaddition followed by a 1,5-sigmatropic shift. The thermal cyclization of **225** with dimethoxyethylene gave **227** as a minor product in addition to **226**. When the reaction of **225** was carried out using 1-deuterio ethyl vinyl ether, it gave **228**. Net 1,7-dipolar cycloadducts are also obtained from **225** and electron-deficient alkenes such as acrylonitrile and methyl acrylate and also dimethyl acetylenedicarboxylate [78ZN(B)216] (Scheme 51).

3-Diazopyrazole **225** readily reacts with electron-rich dipolarphiles of enamines to give 1,7-cycloadducts **232** and **235**. The trisubstituted olefinic dipolarphiles 1-(diethylamino)-2-methyl-1-propene and 1-ethoxy-2-methyl-1-propene were also found to react (83JOC2330) regiospecifically with **225** to give the anticipated derivatives of dihydropyrazolo[5,1-c][1,2,4]triazine **234**. Regiospecific net 1,7-cycloadditions of electronrich olefines and an electron donor acetylene occurred readily (-70 to 10°C) with diazoles having nitrogen in the 2-positions of their azole rings. Di-



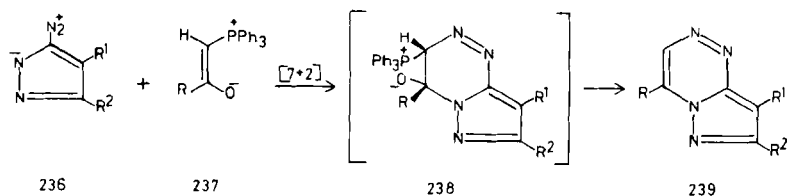
SCHEME 51



SCHEME 52

azoles such as 5-tert-butyl-3-diazo-3*H*-pyrazole and 3-diazo-5-phenyl-3*H*-pyrazole usually add effectively to unsaturated reactants such as enamines, 1-alkoxyalkenes, ketone acetals, aryl isocyanates, norbornene, and norbornadiene to give new 1,7-cycloadducts (87JOC5538). These cyclization reactions may be followed by tautomerization processes leading to new stabilized fused heterocycles or by elimination to novel highly delocalized heteroaromatic derivatives. Addition of activated acetylene to representative 3-diazoazoles also results in regiospecific 1,7-cyclization to give stabilized fused azolo heterocycles **233** (77S556; 87JOC5538) (Scheme 52).

Diazolo[5,1-*c*][1,2,4]triazines **239** were prepared (81JHC675) by cyclizing diazoazoles **236** with acetyltriphenyl-phosphonium methylides. The latter behave as phosphonium enolates **237**, 1-nucleophile-2-electrophiles, rather than the respective tautomers that behave as 1-nucleophile-1-electrophiles. The cyclocondensation was suggested to involve betaines



SCHEME 53

238 resulting from a [7 + 2]- or [11 + 2]-cycloaddition of **236** and **237**, which on elimination of triphenylphosphine oxide gave **239**. No [7 + 1]- or [11 + 1]-cycloadditions took place (Scheme 53).

The coupling of diazotized pyrazoles with the general structure **240** and active methylene compounds is a good method for the synthesis of this ring system. Thus, coupling **240** with benzenesulfonyl acetone or benzene sulfonylacetophenone gave (85JHC453) pyrazolotriazines **242**. Reaction of **240** with ethyl benzenesulfonyl acetate gave hydrazone **241**, which was cyclized thermally or under the influence of acid into **242**. Coupling of **240** with active methylene compounds such as ethyl benzoylacetate or benzoylacetone afforded **243**, which on treatment with an acid gave the pyrazolotriazine **244** [76MI5, 76JMC517, 76T725; 79IJC(B)52; 85JHC453]. They are mild depressants with mild toxicity [79IJC(B)52]. A similar treatment of **240** with phenacyl thiocyanate gave [78ZN(B)216] hydrazone **245**, whose cyclization with sulfuric acid resulted in the elimination of HSCN and the formation of **246**. Coupling of **240** with malononitrile, ethyl cyanoacetate, phenacyl nitrile, nitroacetonitrile, or *N*-hydroxycyanoacetamide gave the respective hydrazones **247**, which readily cyclized to the pyrazolo[5,1-*c*][1,2,4]triazines **248** or **249** in sulfuric acid or acetic acid [76JOC3781; 77JHC227; 78ZN(B)216; 81M245; 83JIC1074; 85KGS682; 88AP141, 88AP851; 89MI2; 90CCC2790].

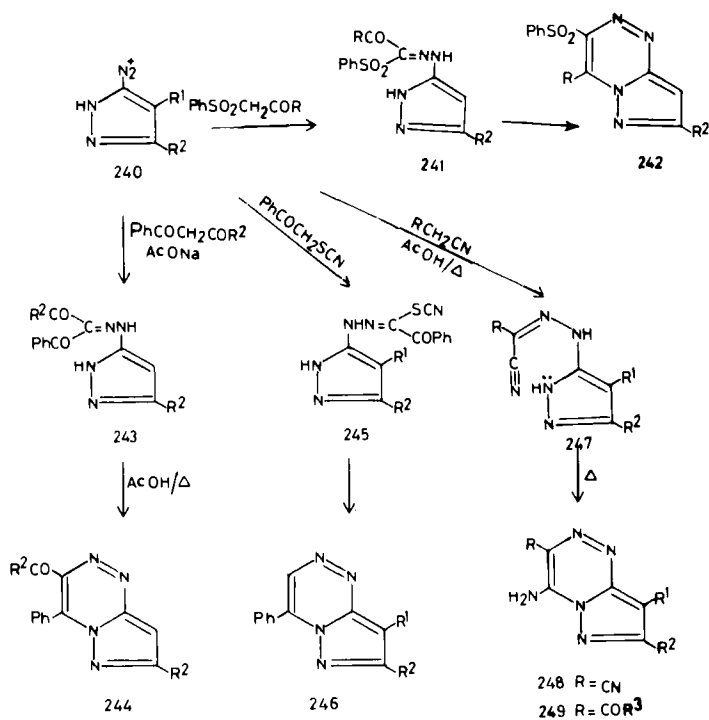
A synthesis of 3,4-bifunctionalpyrazolo[5,1-*c*][1,2,4]triazines has been devised (87JHC1799) by selecting the substituents. Coupling of the diazotized pyrazoles having a 4-aryazo group with ethyl acetoacetate, ethyl cyanoacetate, malononitrile, or phenacyl cyanide gave the respective pyrazolotriazines [79ZN(B)275; 88LA819; 89CCC1082] (Scheme 54).

Pyrazolotriazine **253** was prepared (88JOC887) by coupling 3-diazopyrazole **250** with isopropylidene malonate **251** via **252**. Methylation of **253** with methyl iodide in the presence of methanolic potassium hydroxide gave pyrazolotriazines **255** and **256**, whereas mono *N*-methyl derivative **254** was prepared (88JOC887) by the action of dimethyl sulfate on **253** (Scheme 55).

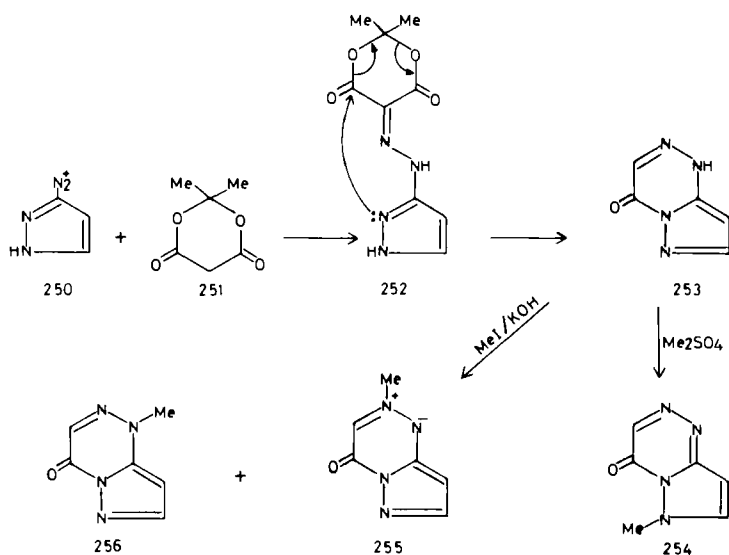
Pyrazol-5-ylazooxazolin-5-one **257** was converted (87MI9) into pyrazolo[5,1-*c*][1,2,4]triazine **258** by treatment with ammonia (Scheme 56).

Coupling the 5-antipyryl derivative of **250** with malonitrile, acrylonitrile, methyl acrylate, methyl methacrylate and dimethyl acetylenedicarboxylate gave the respective pyrazolotriazine (77JHC227; 85MI1, 85MI3). Coupling of a thiadiazole acetonitrile with a diazotized aminopyrazole gave (85LA1962) a pyrazolotriazine having a thiadiazole substituent.

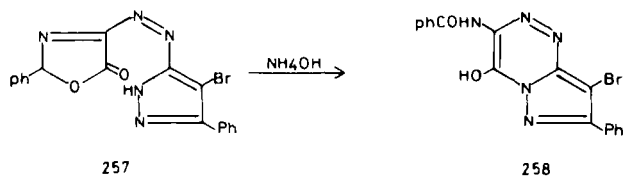
3-Quinoxalinyipyrazolo[5,1-*c*][1,2,4]triazines **264** have been constructed (87JHC1229; 89JHC869) by reaction of the bifunctional heteroaryl diazonium chloride **260** with **259** to give **261** (existing as a mixture of the



SCHEME 54



SCHEME 55

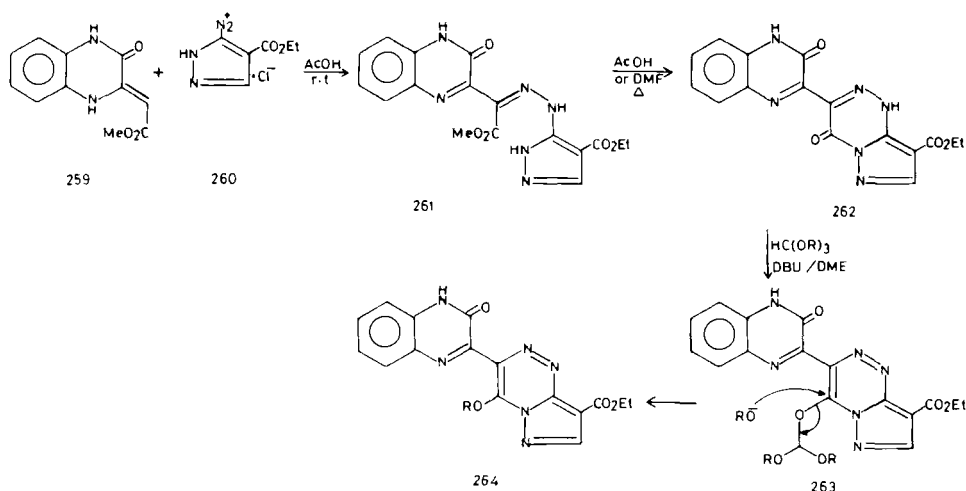


SCHEME 56

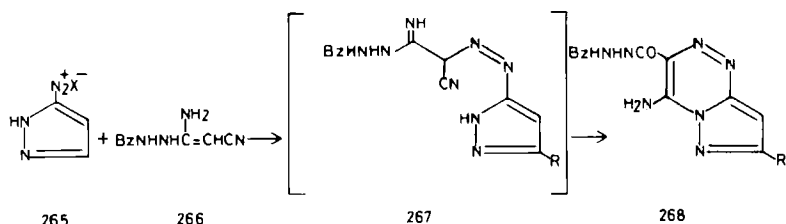
azo and hydrazono tautomers). Heating **261** in DMF or AcOH resulted in cyclization to afford **262**. A better yield of **262** was obtained by heating a mixture of **259** and **260**. Reaction of **262** with orthoesters in presence of DBU gave **264** via **263** (Scheme 57).

Pyrazolotriazines **268** were prepared by coupling **265** with enaminonitrile **266** to give **267** (74M535; 91JPR333), whose thermal cyclization gave **268** (Scheme 58).

The synthesis of pyrazolo[5,1-*c*][1,2,4]triazines was effected (77JHC227; 80JHC209) by the preparation of the hydrazonyl chlorides **269** and **273** by coupling of **240** with 3-chloroacetylacetone and ethyl 2-chloroacetoacetate, respectively. Cyclization of **269** in the presence of sodium acetate gave pyrazolotriazine **270**, which (83JHC285) with sodium hydroxide or thiophenol gave **271** and **272**, respectively. Reaction of hydrazone **273** with hydrazine or phenylhydrazine gave (87AP850) pyrazolotriazines **274** (Scheme 59).



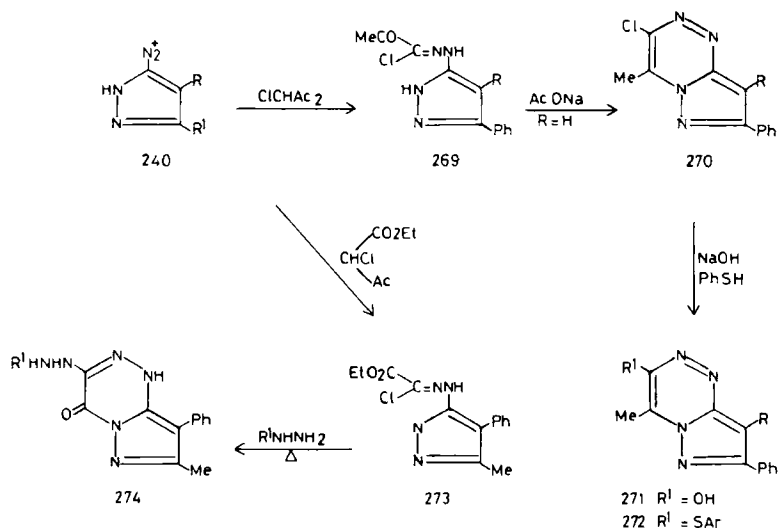
SCHEME 57



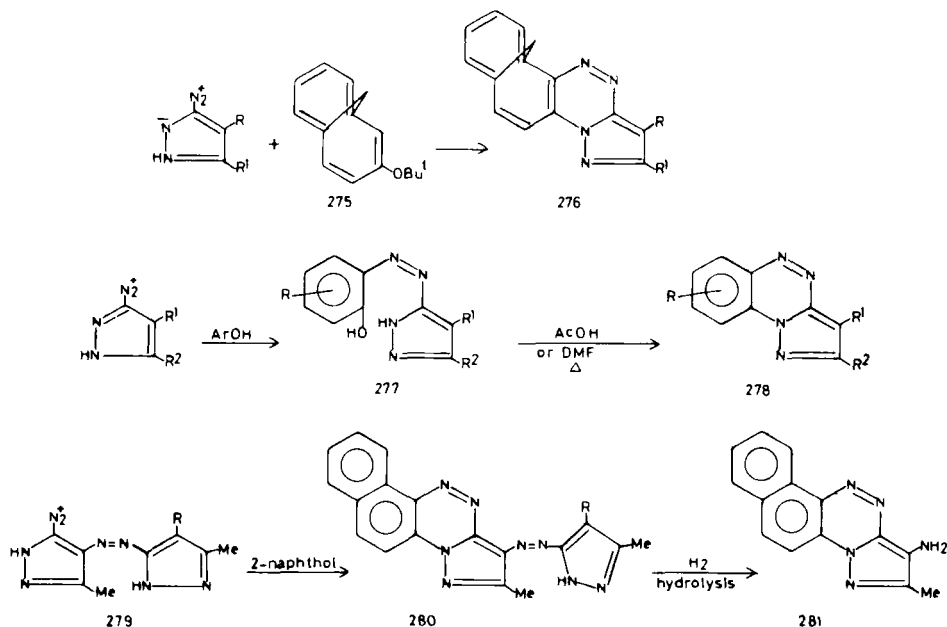
SCHEME 58

Coupling of diazonium betaines with 3-tert-butoxy-1,6-methano[10]annulene **275** under mild conditions led to elimination of tert-butyl alcohol with the formation of methano-bridged triazines **276** (88CB1359).

Pyrazolo[5,1-*c*][1,2,4]benzo- and -naphtho-triazines **278** were prepared (78MI1; 79KGS805; 81M245; 82JHC61; 90CCC2790) by coupling diazotised 3-amino-5-methylpyrazole with resorcinol, phloroglucinol, 2-naphthol, or 1,3- and 2,3-naphthalene diol to give azo compounds **277**, whose intramolecular cyclization took place in boiling AcOH (82JHC61). Azo compounds **277** ($R^1 = R = H$, $R^2 = Me$) could not be cyclized even after 50 h. However, they were cyclized (82JHC61) by heating in ethylene glycol. The reaction was also extended (85MI1) to the antipyryl derivative of the diazotized pyrazole. Similarly, coupling **279** with 2-naphthol gave



SCHEME 59



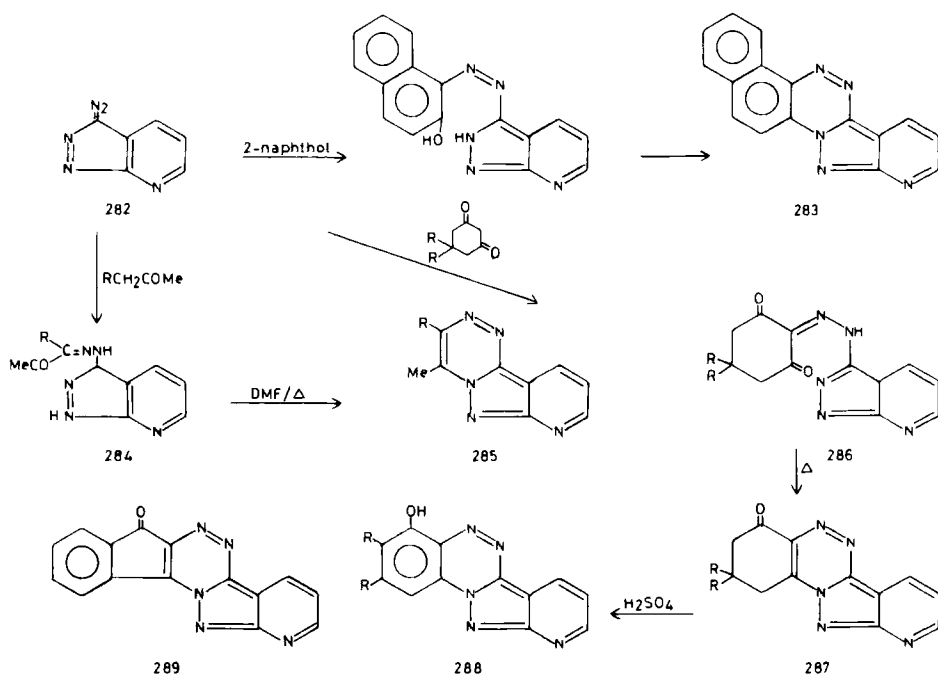
SCHEME 60

280, which were hydrogenated and then hydrolyzed to yield **281** (78KGS382) (Scheme 60).

When 3-diazopyrazolo[3,4-*b*]pyridine **282** was coupled with 2-naphthol it gave the respective azo compound that could be cyclized (78JHC1175) into pentacyclic compound **283**. Reaction of **282** with reactive methylene compounds gave hydrazones **284**, which can be cyclized by heating in an ethanolic or DMF solution or by the action of mineral acids to give **285** [77H681; 78JHC1175; 91IJC(B)878]. Similarly, **287** was prepared via **286**, which on heating or in the presence of concentrated sulfuric acid aromatized to **288**. During the aromatization, a methyl group migrated to the neighboring position (78JHC1175). From indane-1,3-dione, pentacyclic compound **289** was obtained in a similar manner on prolonged heating in sulfuric acid (78JHC1175) (Scheme 61).

Diazotization of 4,5-diphenyl-3-amino-1*H*-pyrazolo[4,3-*c*]pyridazine gave diazonium salt **290**, whose condensation with 2-naphthol gave **291**, which cyclized to **292** (91H901) (Scheme 62).

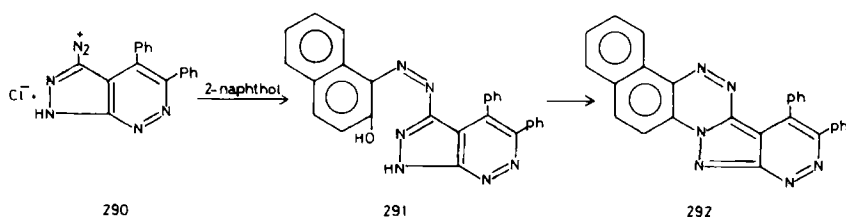
The azolotriazines **294** were prepared (86KGS1137) by heating resorcinol with the corresponding nitroazole **293** in butanol. The pK_a values of some nitropyrazolotriazinones have been calculated (84KGS697). Az-



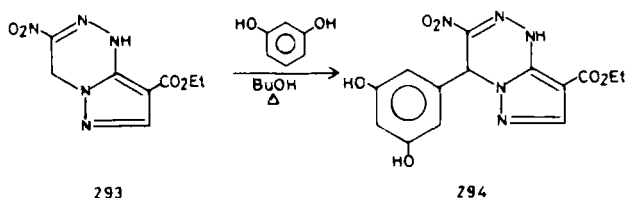
SCHEME 61

olo[5,1-*c*][1,2,4]triazines containing a nitro group as substituent displayed antibacterial and antifungal activities. Structure–activity relationships were reported (90KFZ39) (Scheme 63).

Cyclization of hydrazononitriles **296**, obtained from **295**, with ethanolic sodium hydroxide afforded (76JPR835) pyrazolotriazine derivatives **297**. Alternatively, cyclization of **299** by base afforded **297**, whose reduction with $\text{Na}_2\text{S}_2\text{O}_4$ gave **298** (Scheme 64).



SCHEME 62

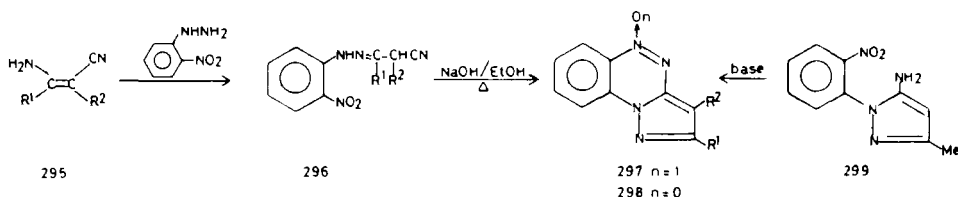


SCHEME 63

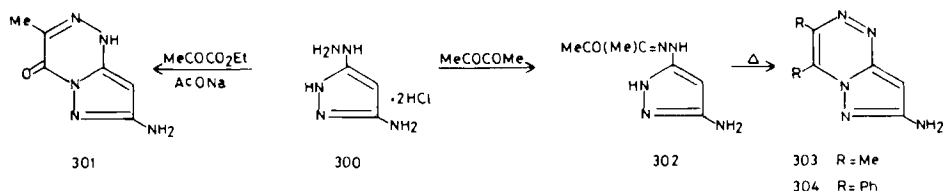
3-Amino-5-hydrazinopyrazole dihydrochloride **300** is a good source for the synthesis of this type of heterocyclic compound [78JCS(P1)885] and it was prepared by reaction of malononitrile with two equivalents of hydrazine. Reaction of **300** with ethyl pyruvate afforded **301**. Unstable hydrazone **302** formed when **300** was boiled with diacetyl rapidly cyclized to **303**. Reaction of **300** with benzil gave **304** directly, which gave an acetyl derivative and resisted reductive deamination. On the other hand, a polymer was isolated from the reaction of **300** with glyoxal (Scheme 65).

4. *Pyrazolo[1,5-d][1,2,4]triazines*

The title compounds were prepared by acylating pyrazole carbohydrazide **306** to give the 1,3,4-oxadiazolyl derivative **308** via **312**, whose rearrangement gave **307**. Alternatively, treating **306** ($R^3 = H$) with triethyl orthoformate gave **307** [73JHC103; 75CR(C)1419; 82JHC817; 91JHC769]. On the other hand, novel pyrazolo[1,5-d][1,2,4]triazin-6-ium-4-olates **305** were prepared from pyrazole carboxylic acid *N*-alkyl hydrazides **306** (80H1291). Cyclization of **306** was also effected with boiling acetic anhydride and benzoyl chloride. The cyclization of **306** into **311** was carried out with ethyl chloroformate (90M12). Reaction of **306** with carbon disulfide followed by methyl iodide gave **309**, whose cyclization gave **310**. Compounds **307**, **311**, and the dimethyl derivative of **310** were pre-



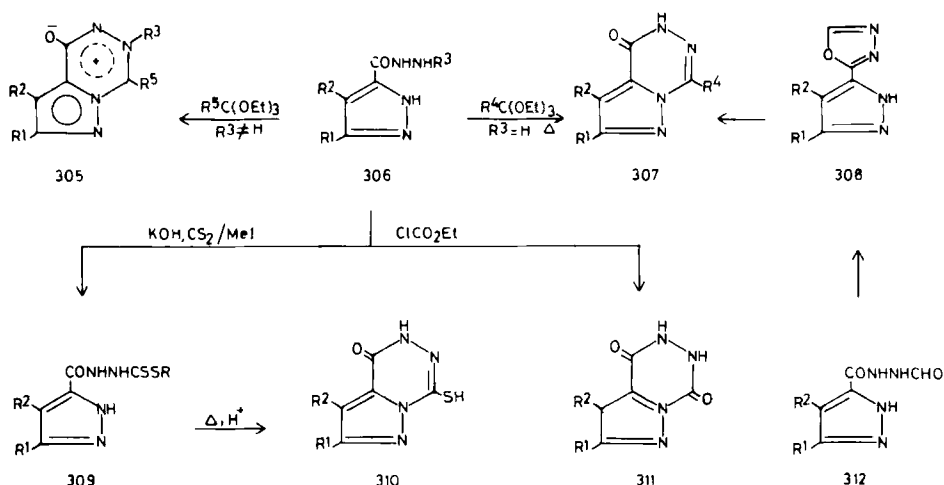
SCHEME 64



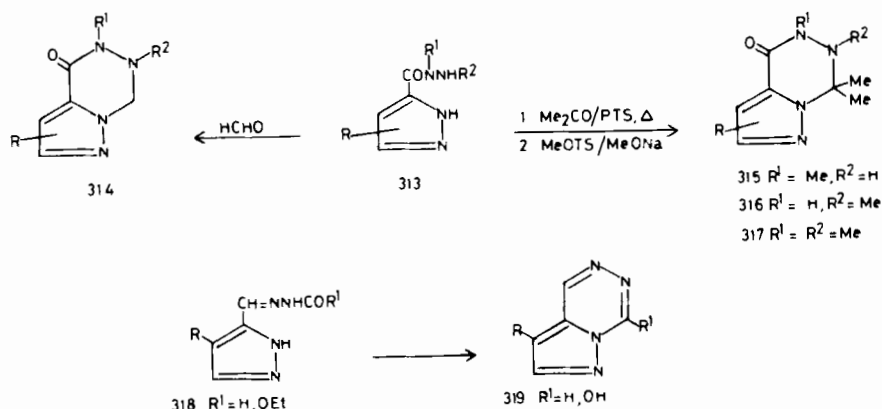
SCHEME 65

pared as anti-inflammatories and anticonvulsants, and they inhibited carrageenan-induced edema (87MIP1; 91JHC769) (Scheme 66).

Reaction of *N'*-monoalkyl and *N,N'*-dialkylpyrazole carboxylic acid hydrazides **313** with formaldehyde gave pyrazolo[1,5-*d*][1,2,4]triazines **314** (89JHC1045). Heating **313** ($R^1 = H$, $R^2 = Ph$) with paraformaldehyde in dioxane followed by heating in dimethyl sulfoxide gave **314** ($R^1 = H$, $R^2 = Ph$). Ring closure of **313** ($R^1 = H$, $R^2 = Me$) with formaldehyde was accompanied by N-5 substitution to give **314** ($R^1 = CH_2OH$, $R^2 = Me$). Cyclization of **313** ($R^1 = H$, $R^2 = Me$) and **313** ($R^1 = Me$, $R^2 = H$) with acetone gave **316** and **315**, respectively [75CR(C)1419; 89JHC1045]. Reaction of **316** with methyl *p*-toluenesulfonate in the presence of sodium methoxide gave **317**. Attempts to convert **315** to **317** by the action of methyl *p*-toluenesulfonate failed. The reaction of **313** with cyclic ketones gave spiro(cycloalkane)-pyrazolotriazines similar to that of **316**



SCHEME 66



SCHEME 67

[75CR(C)1419; 83GEP3242610]; they had a higher therapeutic index as a hypnotic than ketamin.

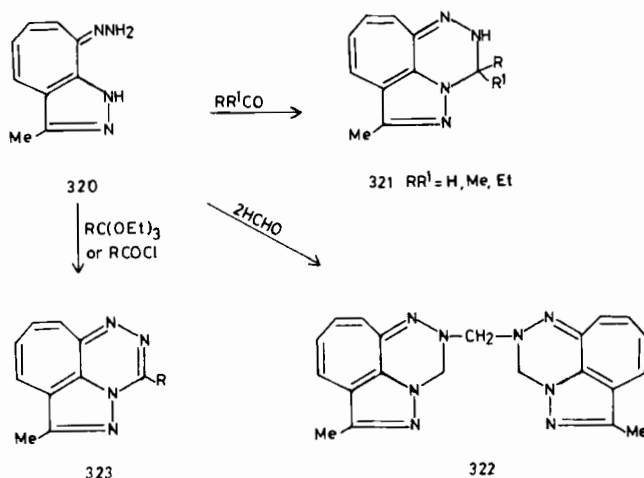
Cyclization of hydrazones **318** gave [75CR(C)1419] pyrazolo[1,5-*d*][1,2,4]triazine **319** (Scheme 67).

2,2a,4,5-Tetraazabenzol[*cd*]azulenes **321** were prepared by treating hydrazone **320** with equimolar amounts of aldehydes or ketones, whereas **322** were formed by reacting **320** with two equivalents of formaldehyde (80S331). Reaction of **320** with orthoesters or acid chlorides afforded **323** (80JHC1057) (Scheme 68).

Reaction of diazopyrazolinones **324** with dimethyl acetylene dicarboxylate gave 1,3-dipolar cycloadducts, which underwent a Van Alphen–Huttel rearrangement to give **325** (82TL2167; 83JOC1069). A similar reaction of **324** with methyl acetylenecarboxylate gave **328** and **329** as regioisomers due to partitioning between **326** and **327** (Scheme 69).

Addition of 2-pyrazolines to tetrazines gave **330** (84AP237; 88CZ17). The pyrazolotriazine derivative **331** was prepared (76MI6) by treating diamino guanidine with acetyl pyruvic acid ethyl ester in either acid or neutral aqueous solution (Scheme 70).

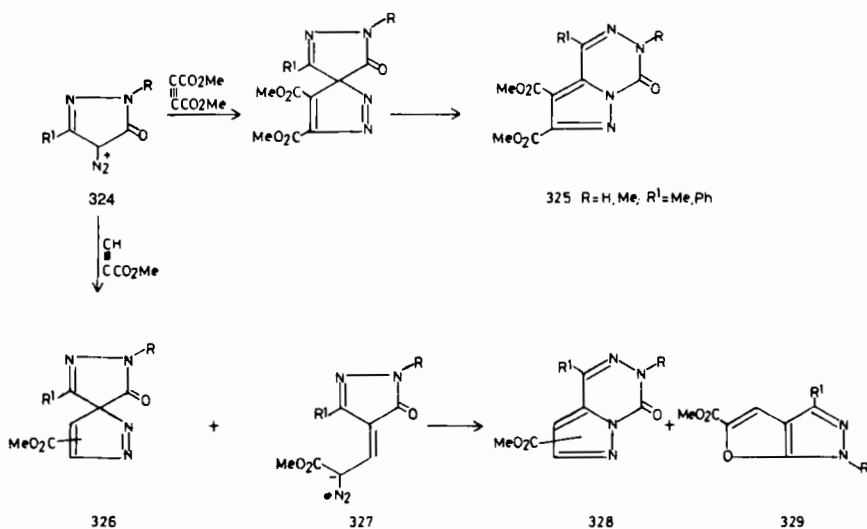
8- β -D-Ribofuranosyl-pyrazolo[1,5-*d*][1,2,4]triazin-4(3*H*)-one **337** was prepared by starting with the ethyl propiolate of D-ribose derivative **332**, whose reduction gave **333**, followed by reaction with diazomethane to give **334**. Reaction of **334** with methyl hydrazinocarboxylate gave **335**, whose cyclization gave **336** and deprotection gave **337** (83MI1) (Scheme 71).



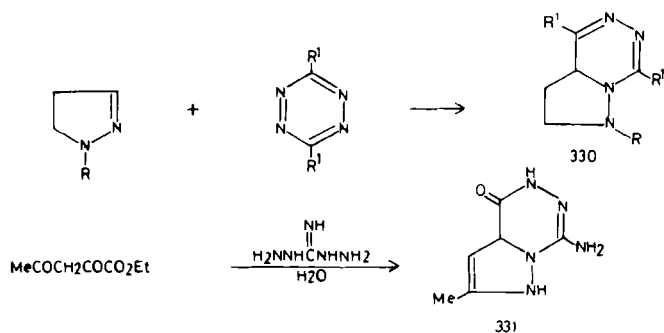
SCHEME 68

5. Pyrazolo[3,4-e][1,2,4]triazines

5-Amino-4-arylazopyrazole **338** reacted with benzoyl isothiocyanate to give the expected pyrazol-5-ylthioureas **339**, which on heating with acetic acid–hydrochloric acid afforded (76JOC3781) pyrazolo[3,4-e][1,2,4]-

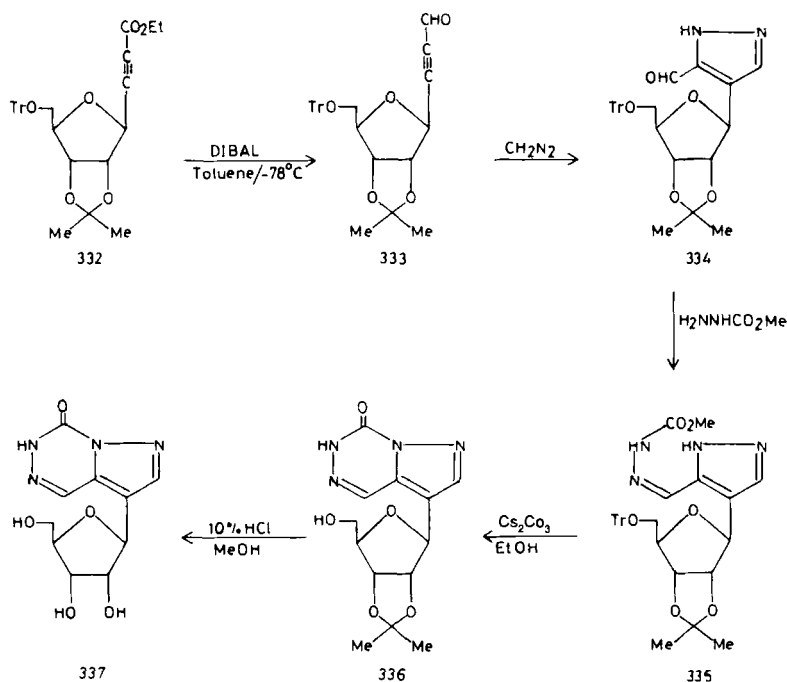


SCHEME 69

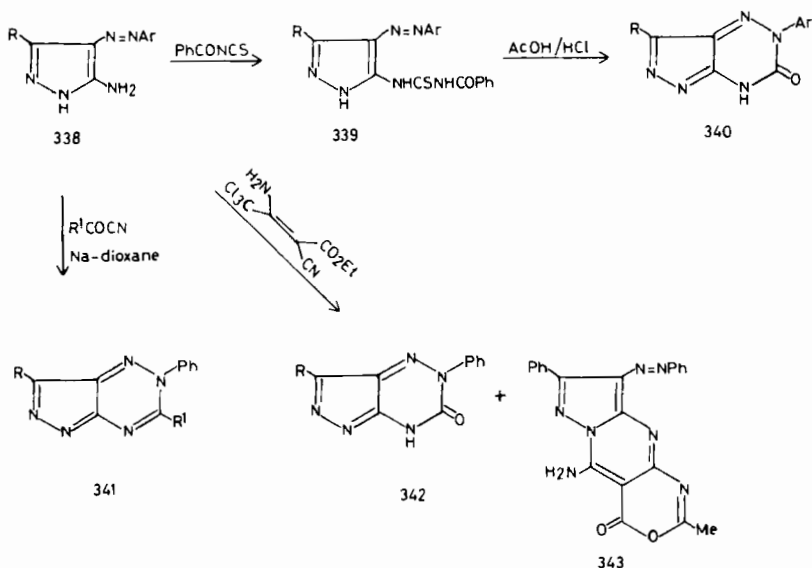


SCHEME 70

triazines **340** in high yields. The cyclocondensation of **338** with acylcyanides gave **341** (89PHA491). The reaction of **338** with an ethylenic nitrile gave **343** in addition to pyrazolo[3,4-*e*][1,2,4]triazine **342** [77ZN(B)-1478]) (Scheme 72).



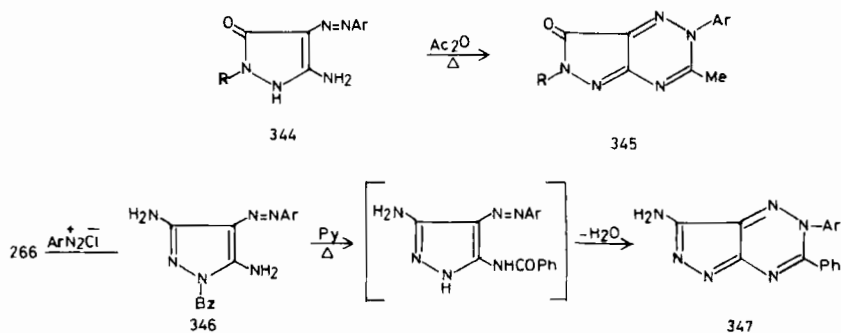
SCHEME 71



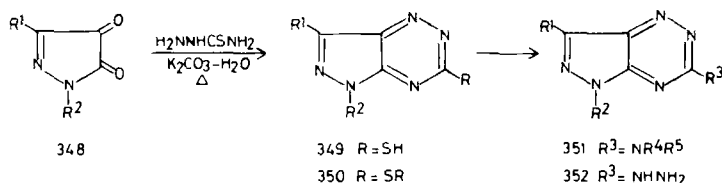
SCHEME 72

Ring system **345** was prepared (90MI6) by boiling **344** with acetic anhydride. It was tested for analgesic activity. Cyclization of pyrazole derivatives **346** gave **347** via migration of the benzoyl group (91JPR333) (Scheme 73).

Cyclocondensation of pyrazole-dione **348** with thiosemicarbazide in the presence of potassium carbonate gave (84JPR994) pyrazolotriazine thione



SCHEME 73



SCHEME 74

349, which reacted with secondary amines to give **351**. Alkylation of **349** with alkyl, aryl, or aralkyl halides gave **350**. Treatment of **350** with hydrazine gave **352**, whose condensation with aldehydes gave the corresponding hydrazones. Derivatives of that ring system were also prepared (88JPR57) by the thermal cyclization of the isothiosemicarbazones or amidinohydrazones of **348** (Scheme 74).

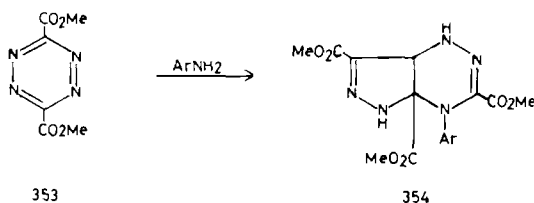
The reaction of dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate **353** with aromatic amines gave (82CB683) pyrazolo[3,4-*e*][1,2,4]triazines **354** (Scheme 75).

Previous methods involved the construction of the triazine onto a pyrazole ring with suitable functionality. On the other hand, the reverse construction is also possible. Thus, **356** was prepared (87MI8) from **355** with hydrazine. The stability of **356** to dilute acids and bases was studied (87MI8) (Scheme 76).

6. Pyrazolo[4,3-*e*][1,2,4]triazines

Treatment of 5-(dichlorophenylmethyl)-3-phenyl[1,2,4]triazin-6(1*H*)-one **357** or the respective ketone with hydrazine or phenylhydrazine gave **358**, which were cyclized with acetic acid to pyrazolo[4,3-*e*][1,2,4]triazines **359** (84PHA504; 85MI2) (Scheme 77).

Condensation of 1,3-diphenyl[1,2,4]triazin-6-one **360**, obtained from reaction of hippuric acid and phenylhydrazine, with aromatic aldehydes



SCHEME 75

or ketones gave 5-arylidene[1,2,4]triazinones **361**, which reacted with phenylhydrazine to give tetrahydropyrazolo[4,3-*e*][1,2,4]triazines **362** [82IJC(B)115] (Scheme 78).

Pyrazolo[4,3-*e*][1,2,4]triazines **365** were prepared (80JHC209) by treatment of 4-bromo-3-phenylpyrazol-5-ylhydrazonyl chlorides **364**, obtained from **363**, with hydrazine or phenylhydrazine. It should be noted that the reaction of 3-phenylpyrazol-5-ylhydrazonyl chloride gave (77JHC227) pyrazolo[1,5-*c*][1,2,4]triazine (Scheme 79).

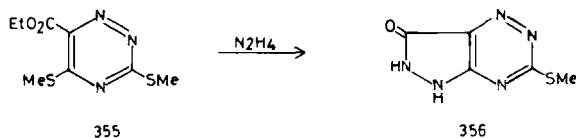
B. [1,2,4]TRIAZINO[*x,y-z*]INDAZOLES

1. [1,2,4]Triazino[4,3-*b*]indazoles

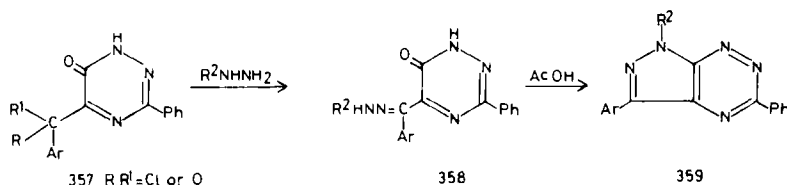
3-Substituted 4-amino[1,2,4]triazino[4,3-*b*]indazoles **368** were obtained (76CCC3090) in good yields from the cyclization of hydrazones **367**, which were obtained by coupling of indazole-3-diazonium chloride **366** with malononitrile, ethyl cyanoacetyl carbamate, 2-cyanomethylbenzimidazole, and methyl cyanoacetate. The cyclization was so easy with hydrazones **367a–367c** that heating them in ethanol or acetic acid for a short time was sufficient. By contrast, cyclization of the hydrazone **367d** necessitated heating acetic acid for several hours. Derivatives **370** and **371** were prepared (87MI1) from **366** by treatment with sulfonyl methylene compounds. Indazolo[3,2-*c*][1,2,4]benzo- and naphtho-triazines **369** were prepared (78MI2) by coupling **366** with resorcinol, phloroglucinol, 2-naphthol, or 1,3-dihydroxynaphthalene and cyclizing the azo compounds in HCl or AcOH (Scheme 80).

The [1,2,4]triazino[4,3-*b*]indazoles **372** (*X* = CH) were prepared (81JHC675) by cycloaddition of **366** (*X* = CH) with acylphosphonium ylids. Diaza analogue **372** (*X* = N) was prepared in a similar manner (Scheme 81).

Diazotized 3,6-diamino-4-phenylpyrazolo[3,4-*b*]pyridine-5-carbonitrile **373** reacted with 2-naphthol to give **374** and with active methylene com-



SCHEME 76



SCHEME 77

pounds as well as dimethyl acetylenedicarboxylate to afford polyaza heterocycles **375** (91G209) (Scheme 82).

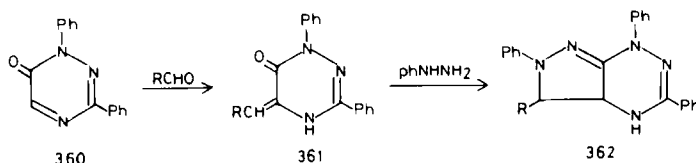
Cycloaddition of diazoindazole **376** with acetylenic compounds afforded (77S556; 78CB2258) triazinoindazoles **377**. The synthesis of the diaza analogue of **377** was also successful (Scheme 83).

2. [1,2,4]Triazino[4,5-b]indazoles

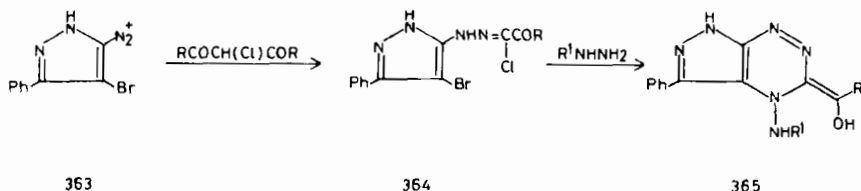
2*H*,3*H*[1,2,4]Triazino[4,5-*b*]indazole-1,4-dione **380** was obtained (78JHC1159) by thermal cyclization of indazole-3-carbethoxyhydrazide **379**. Compound **380** underwent rearrangement (83JHC427) to the indazolyl oxadiazolone derivative upon electron impact in mass spectra. Treatment of **378** with triethyl orthoformate gave **384** via **383**. Treatment of **384** ($X = O$) with P_4S_{10} gave **384** ($X = S$), which on desulfurization gave **381** which on dehydrogenation gave **385**. Rearrangement of 3-oxadiazolylindazoles **382** gave **384** (79JHC53; 84JHC91) (Scheme 84).

C. [1,3]DIAZOLO[x,y-z][1,2,4]TRIAZINES

There are nine possible isomeric structures representing different annulations onto the triazine ring to form [1,3]diazolo[x,y-z][1,2,4]triazines. Only eight are reported during the period covered by this review.



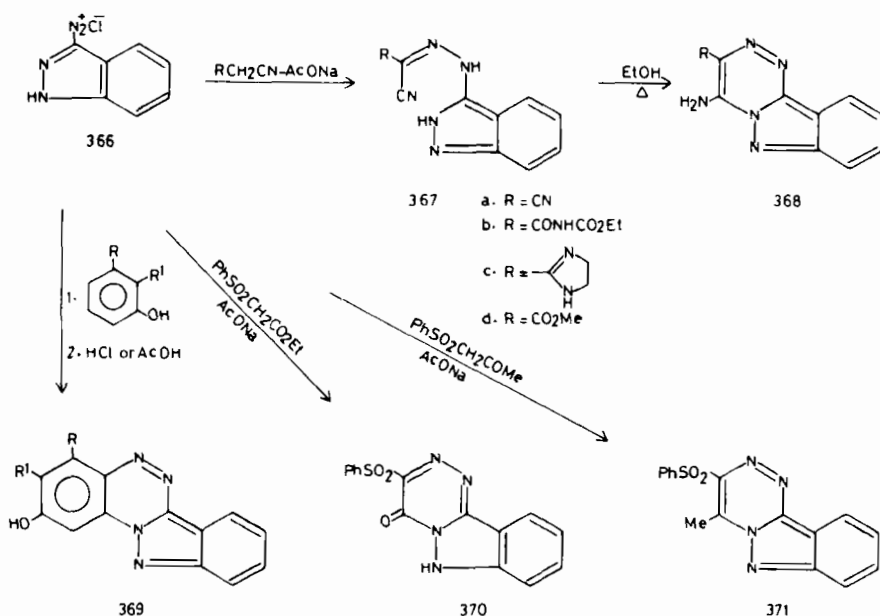
SCHEME 78



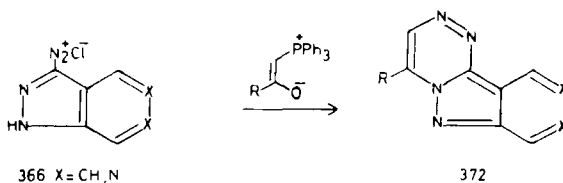
SCHEME 79

1. Imidazo[1,2-*b*][1,2,4]triazines

The skeleton of this ring system was prepared by constructing the imidazole ring onto a suitably functionalized triazine ring. The 3-amino derivatives of [1,2,4]triazines are readily available starting materials. Parent imidazo[1,2-*b*][1,2,4]triazine **387** was found to be the product of heating 3-amino[1,2,4]triazine **386** in concentrated hydrochloric acid. Its structure was determined by X-ray diffraction analysis [76RTC74; 77AX(B)274]. The ^{15}N chemical shifts of this ring system were correlated with the degree of contribution to the ground state of those resonance structures that place



SCHEME 80



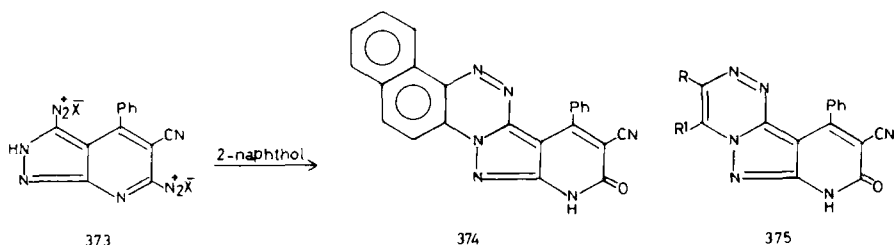
SCHEME 81

a partial positive charge on the bridgehead nitrogen atom (82OMR87) (Scheme 85).

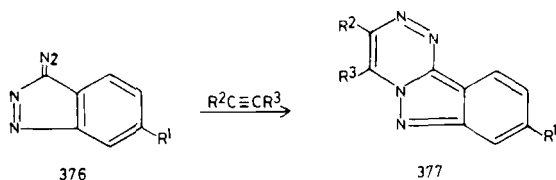
3,6-Disubstituted imidazo[1,2-*b*][1,2,4]triazines **388** were prepared [77IJC(B)607] by reacting aminoguanidine bicarbonate with the respective monobromoketone. Reaction of 3-amino-5,6-disubstituted triazines **389** with phenacyl bromides at ambient temperature gave **390**, whose cyclocondensation to give **391** was achieved thermally (76UKZ1166; 79KGS1561; 84MI1, 84UKZ1111; 86PHA812; 87UKZ1095). Some were tested for antitumor activity (86PHA812). 3,6-Diaryl-7-arylazoimidazo[1,2-*b*][1,2,4]triazines **392** were obtained (86JFC299) by treating **389** with α -oxo-*N*-aryl- α -arylethanehydrazonoyl bromides. When the phenacyl bromides reacted with formamidine **393**, imidazo[1,2-*b*][1,2,4] triazines **394** were obtained (87MI8). They were screened against P388 lymphocytic leukemia in mice and were found inactive (Scheme 86).

Triazines **396** were obtained (79KGS1561) by treating **395** with α -halogeno esters. Hydrolysis of **396** to the corresponding acid followed by cyclization with acetic anhydride gave imidazo[1,2-*b*][1,2,4]triazine **398**, whose condensation with aldehydes or ketones gave **399**. Compounds **399** ($R^2 = \text{H}$) were also obtained from reaction of **396** with aldehydes. Heating **396** with acetic anhydride gave **397**.

Alkylation of **395** with α -bromoacetaldehyde acetal (80MI1) or 2-bromoethanol (79KFZ61) gave alkylated derivatives **400** and **402**, re-



SCHEME 82



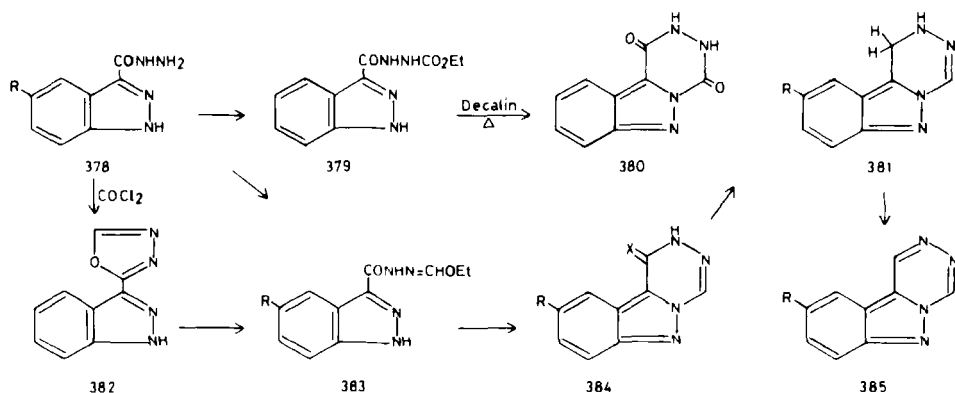
SCHEME 83

spectively. Their cyclization gave **401**. Treatment of **395** with ethylene dibromide gave another preparation. None of the compounds had herbicidal activity (80MI1) (Scheme 87).

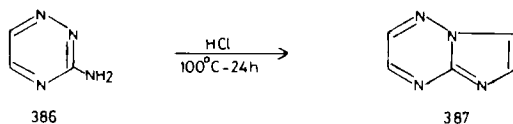
Similarly, bromoacetaldehyde ethylene acetal with 3-aminobenzo [1,2,4]triazines **403** gave (82JHC61) linear tricyclic imidazobenzo[1,2,4] triazines **404** (Scheme 88).

Instead of using an amino group at the 3-position of the triazine ring, the introduction of the required three atoms of the imidazole ring was achieved by the displacement of a suitable substituent at the 3-position by a functionalized amine. Thus, 3-(2-hydroxyethylamino)[1,2,4]triazines **406** were obtained from **405** by reaction with ethanolamine. Treating **406** with thionyl chloride afforded 3-(2-chloroethylamino)[1,2,4]triazines **407**, which on cyclization with potassium-*tert*-butoxide yielded a mixture of **408** and **409**. Dehydrogenation of **409** gave **410**. Isomerization of **408** with sodium iodide gave **409** (76JHC807) (Scheme 89).

Amination of triazine derivative **412**, obtained from **411**, with propargylamine gave **413**, which was cyclized to give (89CZ252) imidazotriazine **414** (Scheme 90).



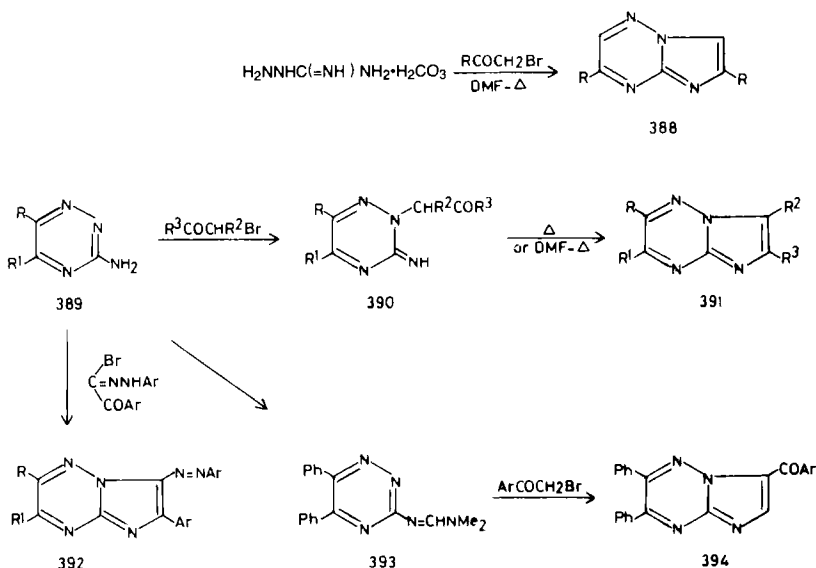
SCHEME 84



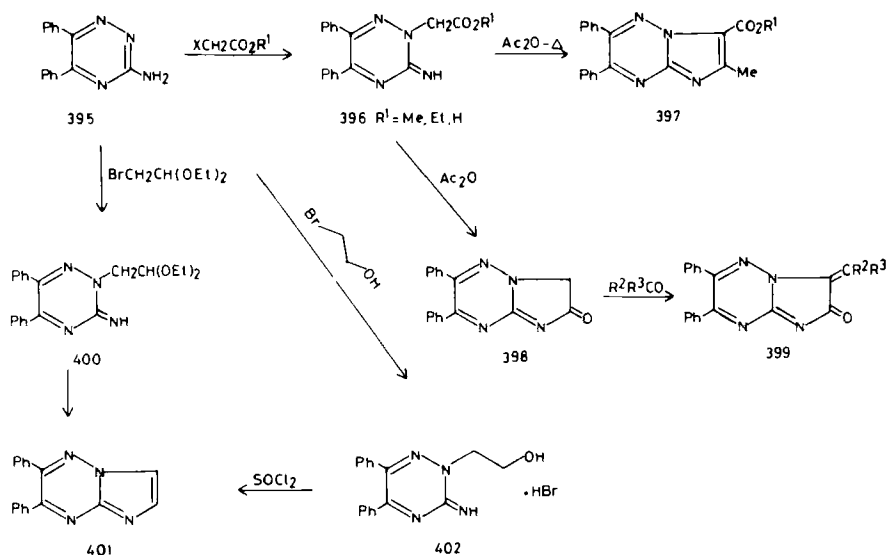
SCHEME 85

The synthesis of this ring system also may be achieved by constructing the triazine ring onto an imidazole ring as in the reaction of **415** with unsymmetrical dicarbonyl compounds such as phenylglyoxal hydrate to afford (74JHC327) a mixture of 2- and 3-phenylimidazo[1,2-*b*][1,2,4]triazines **416** and **417**. However, in order to avoid the formation of mixtures, the reaction was conducted on substituted glyoxaldoximes, whose treatment with **415** in the presence of hydrochloric acid led to imidazo[1,2-*b*]triazine **419** in high yield (75MI7). The interaction of **415** with α -ketoacids in acid afforded (74JHC327; 76MI3, 76URP531807) 4*H*-imidazo[1,2-*b*][1,2,4]triazin-3-ones **418**. Cyclocondensation of **415** with ethyl oxalate gave 2,3-dioxoimidazotriazine **420** (79UKZ82) (Scheme 91).

Imidazo[1,2-*b*]acenaphtheno[1,2-*e*][1,2,4]triazines **423** and **424** were prepared (78KGS1565) in a manner similar to that used for simple com-



SCHEME 86

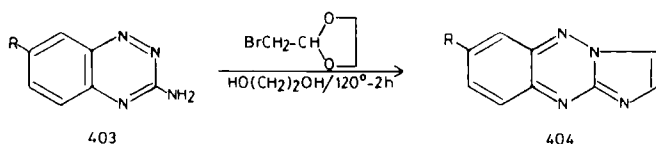


SCHEME 87

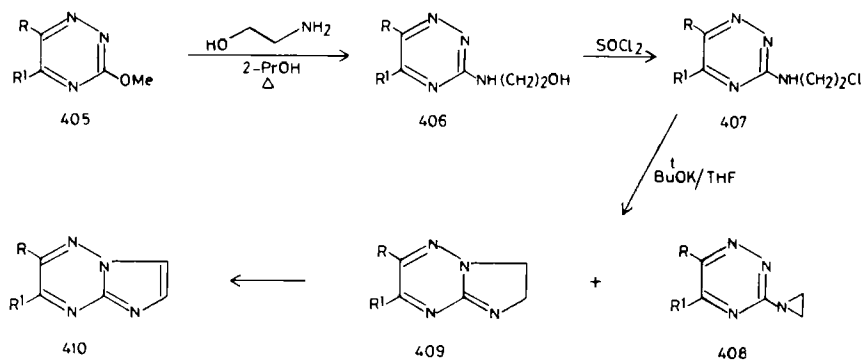
pounds by reaction of acenaphthenequinone **421** with **422** or by reacting 3-aminoacenaphthenotriazine **426** with phenacyl bromide or ethyl bromoacetate followed by cyclization (82ZOR2602) (Scheme 92).

Imidazo[1,2-*b*][phenanthreno[9,10-*e*][1,2,4]triazines **428** were prepared by cyclocondensation of diaminoimidazoles **422** with 9,10-phenathrenedione **427** (83URP668274, 83URP552792). Cyclocondensation of **429** with α -bromocyclohexanone gave **430** (79URP703530; 84ZOR1345) (Scheme 93).

Chemical modification on the ring was also used for the synthesis of functionalized derivatives. 3-Chloroimidazo[1,2-*b*][1,2,4]triazines **432** were prepared by reacting **431** with $SOCl_2-CHCl_3$ containing a catalytic quantity of DMF, whereas the use of $POCl_3-PCl_5$ gave a mixture of mono and dichloro derivatives. The reactivity of **432** toward amines to give **433** was studied (86KGS981). Bromination, formylation, hydroxymethylation,



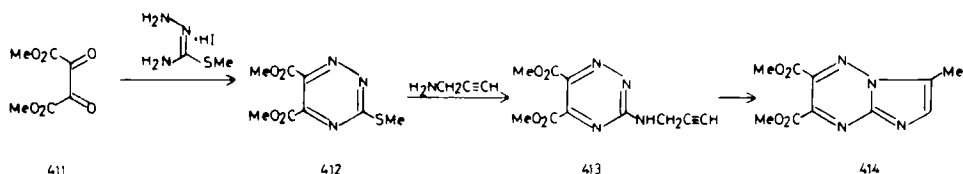
SCHEME 88



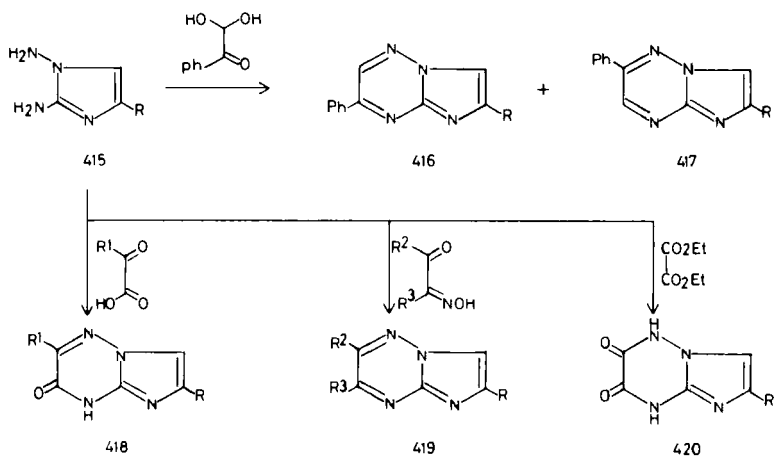
SCHEME 89

and nitration of 6-aryl-2,3-diphenylimidazo[1,2-*b*][1,2,4]triazines occurred at C-7 in agreement with MO calculations (CNDO/2) (84KGS413). Hydroxymethylation of **434** with formaldehyde in the presence of acetic acid gave (84KGS1565) a mixture of four products **435**. Reaction of perchlorate **436** with triethyl orthoformate gave the condensation product **437** (80UKZ389) (Scheme 94).

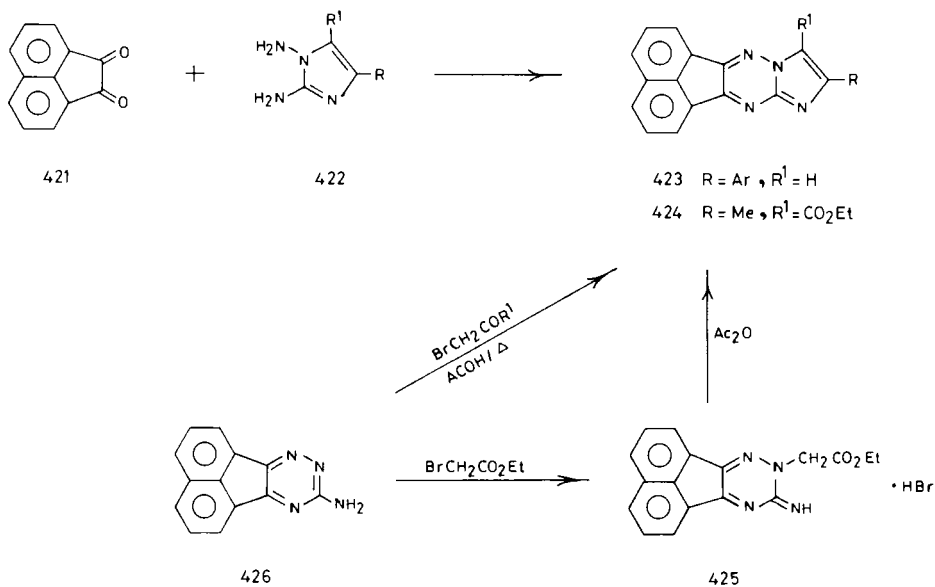
2,6-Disubstituted imidazo[1,2-*b*][1,2,4]triazin-3-ones exist in the solid state and in aprotic solvents in the lactam form, but in hydroxylic solvents they form stable hydrogen bonds (79ZOR1991). The site of protonation of derivatives was determined (91MRC468) to be on the imidazo nitrogen. Basicity and UV spectral characteristics of imidazo[1,2-*b*][1,2,4]triazines were determined (87UKZ325). Imidazo[1,2-*b*]tetrahydrobenzo[1,2,4]triazines are useful as luminophors (83URP668274). The luminescence spectra of imidazo[1,2-*b*][1,2,4]triazines showed that the substituents on the imidazole ring had a greater effect on the intensity than those on the triazine ring. A large increase in intensity occurred in the case of tetraphenylimidazotriazine. Electron-donating substituents tended to increase the intensity whereas electron-accepting substituents quenched it (79MI1). Laser action was achieved on the imidazotriazine (imitrine) under excitation by the third (355 nm) and fourth (266 nm) harmonics of the Nd laser and the



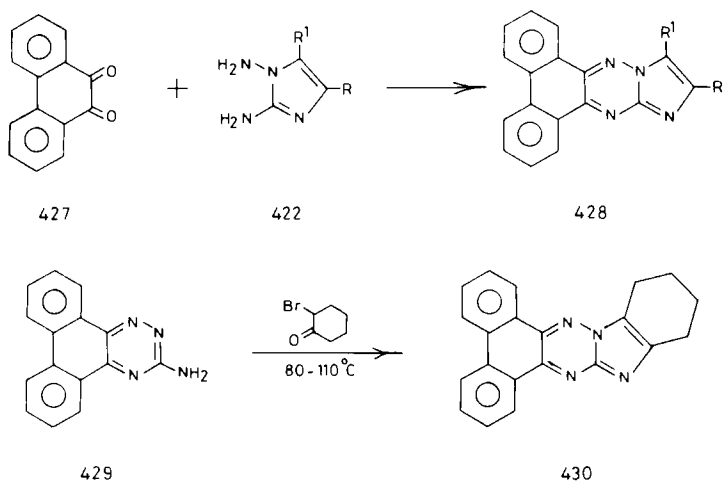
SCHEME 90



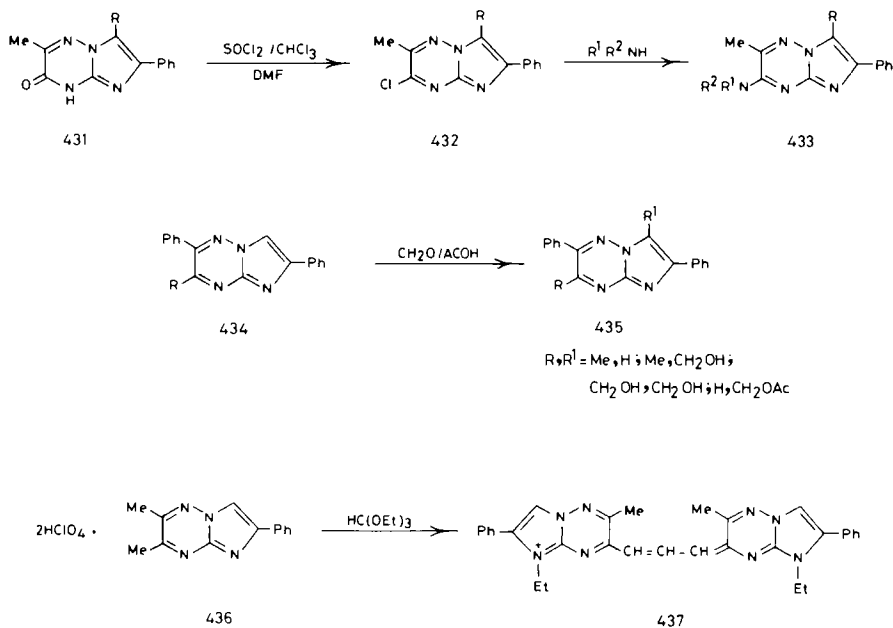
SCHEME 91



SCHEME 92



SCHEME 93



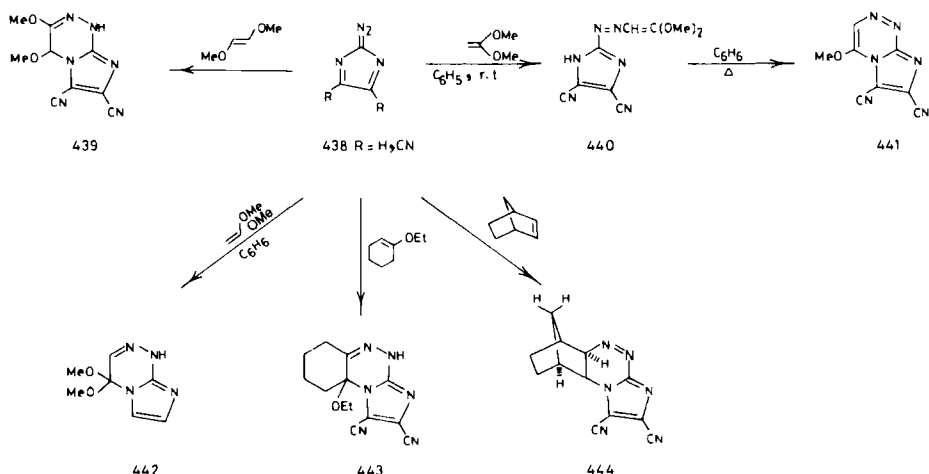
SCHEME 94

influence of substituents on the light resistance of these dyes during irradiation was studied (80MI6, 80MI7; 87UKZ1197).

2. Imidazo[2,1-c][1,2,4]triazines

Methods for the synthesis of this ring system are mostly through the construction of the triazine ring onto an imidazole. 2-Diazoimidazole **438** was used as a starting material; its involvement in a 1,7-cycloaddition process proved to be a useful method for constructing the triazine ring. The reaction of **438** with 1,1-dimethoxyethylene gave the imidazotriazine **442**, whereas heating of **438** with 1,1-dimethoxyethylene afforded **441** (86CC1127; 87JOC5538). The latter reaction at room temperature gave **440**, whose thermal cyclization gave **441** (84CC295). Reaction of **438** with 1,2-dimethoxyethene gave **439** [90JCS(P2)1943]. Similarly, reaction of **438** with either 1-ethoxycyclohexene or norbornene gave (87JOC5538) adducts **443** and **444**, respectively.

The energies of several intermediates that could arise from the reaction of diazoazoles with alkenes have been estimated [90JCS(P2)1943] by means of the MNDO, AMI SCF-MO, and *ab initio* methods. The calculations suggest a 1,4-dipole behavior (also viewed as a 1,7-dipole) for most diazoazoles when reacting with electron-rich alkenes; it is believed that the approach between **438** and alkenes is asynchronous. On the basis of that study, some errors have been corrected (Scheme 95).



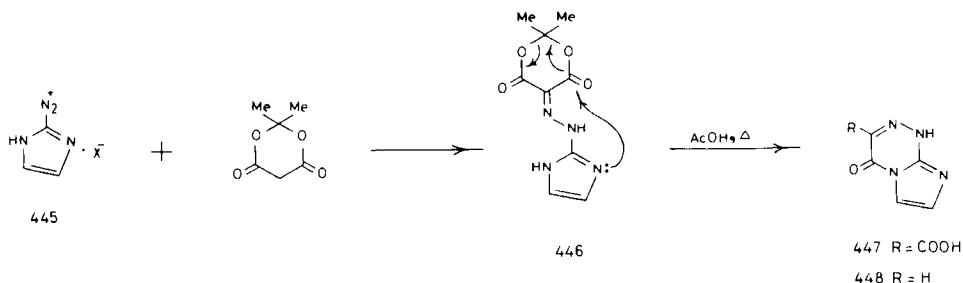
SCHEME 95

Coupling of 2-diazoimidazole **445** with meldrum's acid occurred instantaneously to give hydrazone derivative **446**. Cyclization and decarboxylation could be carried out in one pot by heating in acetic acid to afford (88JOC887) imidazotriazine **447**, which on further heating gave **448**. Methylation of **448** under basic conditions takes place exclusively on N-1 and N-2. In the absence of base, a complex mixture may be obtained (Scheme 96).

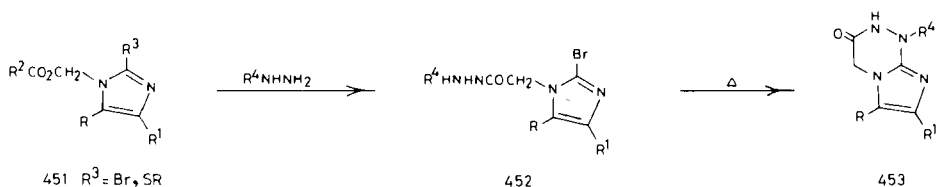
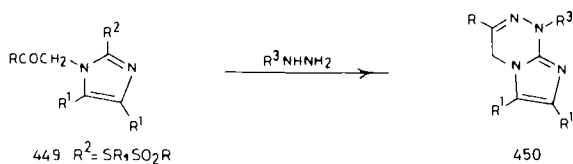
The two nitrogen atoms of the triazine ring could be introduced by the reaction of hydrazines with phenacyl derivatives of imidazoles having a leaving group on the 2-position. Thus, condensation of **449** with hydrazines gave **450** (75MI3; 77JHC59). The synthesis of 3-oxo-imidazotriazines **453** was also carried out by (76KGS1424; 77JHC59) the condensation of ester derivative **451** with hydrazine. Intermediate hydrazone **452** could be isolated by carrying out the reaction at lower temperatures. Selective ethylation on the oxygen of **453** was achieved in presence of triethyloxonium fluoroborate. The corresponding benzo and naphtho analogues of **453** could be prepared in a similar manner (76KGS1424) (Scheme 97).

Again, the hydrazine was used as a cyclizing agent for N-functionalized imidazoles such as **454**, whereby tetrahydro derivative **455** was obtained (75KGS422; 75MI3; 77URP555098). Triazin-4-ones **457** and their dihydro derivatives were prepared (76URP502888; 77JHC59) by treating 2-hydrazinoimidazoles **456** with α -oxoacids or esters. Cyclocondensation of 2-hydrazino-2-imidazoline hydroiodide **458** with dimethyl acetylenedicarboxylate gave imidazotriazinone **459** (84GEP3302413), whose herbicidal action was tested. Chromium trioxide oxidation of **459** gave **460** (Scheme 98).

Construction of the imidazole ring onto a triazine has been also used for the synthesis of this group of compounds. The reaction of 3-aminobenzo[1,2,4]triazine with α -bromoacetaldehyde acetal gave the [1,2-*b*] linear isomer. On the other hand, the similar reaction on 1-oxide **461**



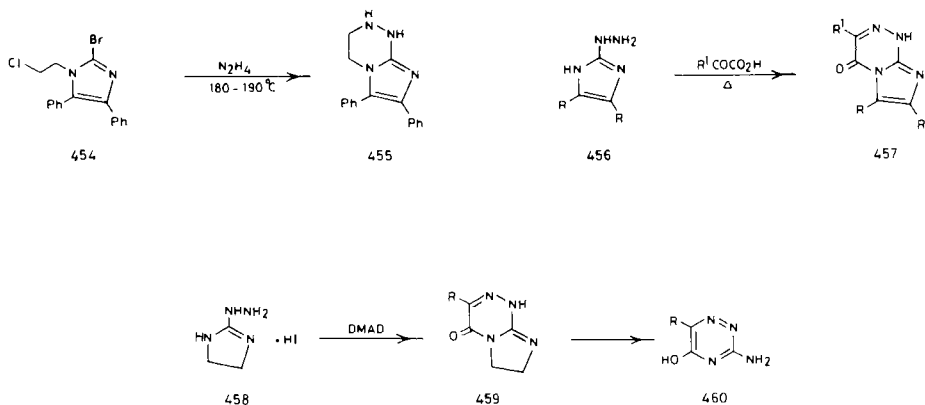
SCHEME 96



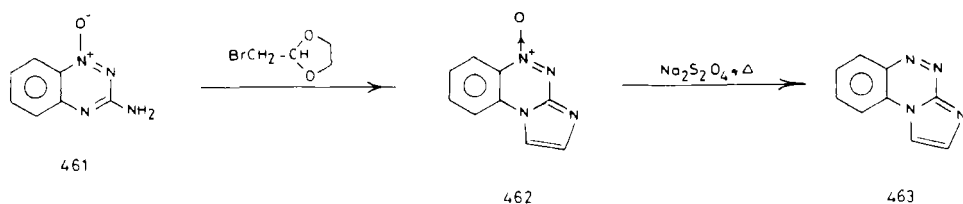
SCHEME 97

gave (82JHC61) the angular [2,1-*c*] isomer **462**, which was converted to **463** by sodium dithionite (Scheme 99).

The absorption and luminescence spectra of imidazo[1,2,4]triazines and related compounds were recorded. The phenyl groups on both the 6-and the 7-positions quenched the luminescence. An acceptor substituent such as CHO in position-7 sharply reduced the luminescence quantum yield (82MI4). A detailed study of the infrared spectra of imidazotriazines was carried out (75T433).



SCHEME 98



SCHEME 99

3. Imidazo[5,1-c][1,2,4]triazines

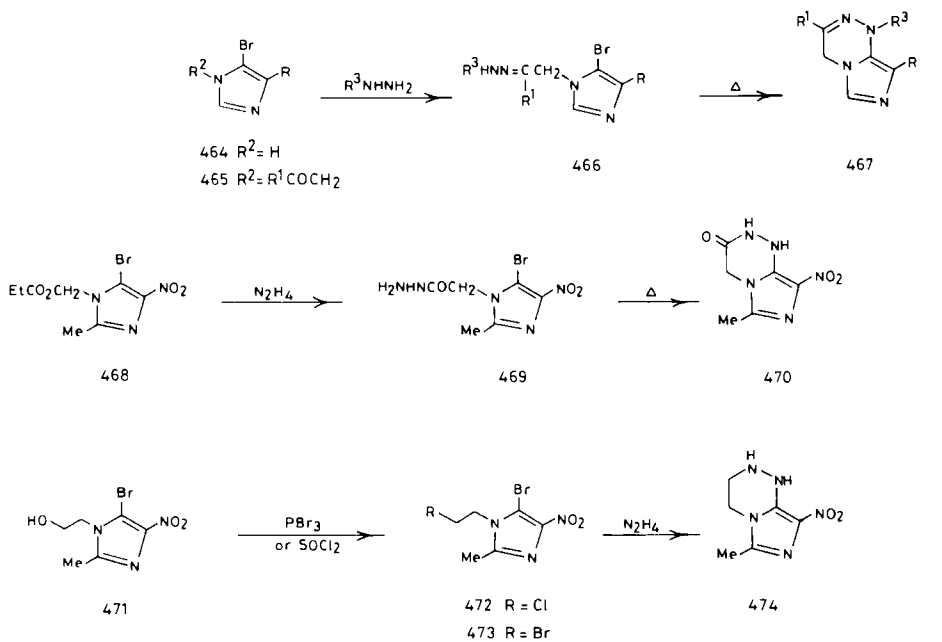
Few examples are reported for this ring system. Cyclocondensation of **465** with hydrazines gave **467** (74KGS1696; 75KGS855; 81KGS833) via the formation of the hydrazone **466** and subsequent cyclization. The required functionality in **465** could be achieved either by alkylation of imidazole derivatives with phenacyl bromide followed by bromination or by reacting bromo derivative **464** or its sulfonyl analogue with phenacyl bromide. On the other hand, reaction of **468** with hydrazine gave hydrazide **469**, which cyclized on heating to give **470**.

1,2,3,4-Tetrahydroimidazo[5,1-c][1,2,4]triazine **474** was prepared (79KGS1540) by treating imidazole derivatives **472** or **473** with hydrazine. Compound **473** was obtained by reaction of the respective imidazole with 1,2-dibromoethane or by the reaction of the alcohol derivative **471** with phosphorus tribromide. On the other hand, chlorination of **471** with thionyl chloride gave **472** (Scheme 100).

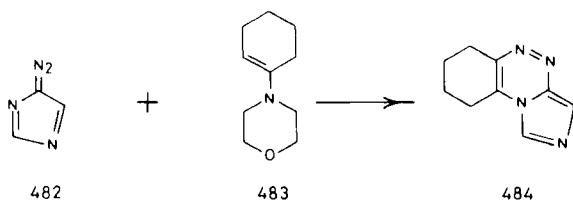
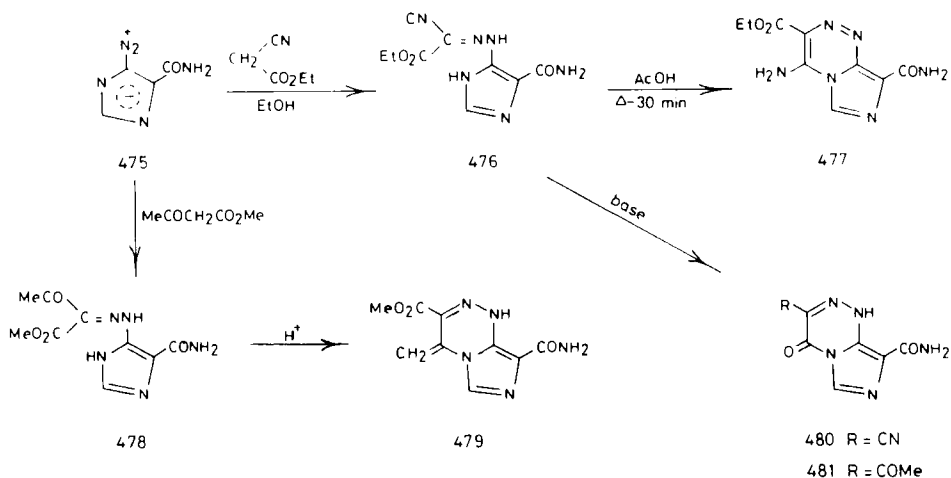
Diazo coupling was also used for the synthesis of this ring system. 3-Diazoimidazole **475** was coupled with ethyl cyanoacetate to give imidazolyl hydrazone **476**, which cyclized to triazine **477** on boiling in acetic acid. Reaction of **475** with methyl acetoacetate gave **478**, which underwent acidic dehydration to give **479**. On the other hand, base treatment of **476** and **478** gave imidazotriazines **480** and **481**, respectively [81JCS(PI)1424].

The reaction of 1-morpholinocyclohexene **483** with diazoimidazole **482** had taken place by 1,7-cycloaddition, followed by subsequent elimination of morpholine to yield (87JOC5538) imidazotriazine derivative **484** (Scheme 101).

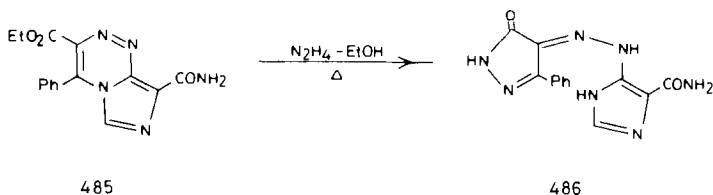
The reactivity of 4-phenylimidazo[5,1-c][1,2,4]triazin-8-carboxamide **485** toward hydrazine has been studied [82JCS(PI)1811], whereby pyrazol-4-ylidenehydrazino)imidazole-4-carboxamide **486** was formed (Scheme 102).



SCHEME 100



SCHEME 101



SCHEME 102

4. *Imidazo[1,2-d][1,2,4]triazines*

Imidazo[1,2-d][1,2,4]triazines **488** were prepared (78USP4096257) from the reaction of 2-imidazocarboxylic acid hydrazide **487** with orthoesters. They inhibited cyclic-AMP phosphodiesterase in the mouse skin phosphodiesterase test and had antiasthina.

Alternatively, imidazotriazine **491** was prepared [89JCR(S)206] by the thermal cyclization of carbethoxy hydrazone **490**, which was prepared from carbaldehyde acetal **489**. The latter was prepared by cyclocondensation of the respective phenacylamine hydrochloride with diethoxy acetonitrile in the presence of sodium methoxide.

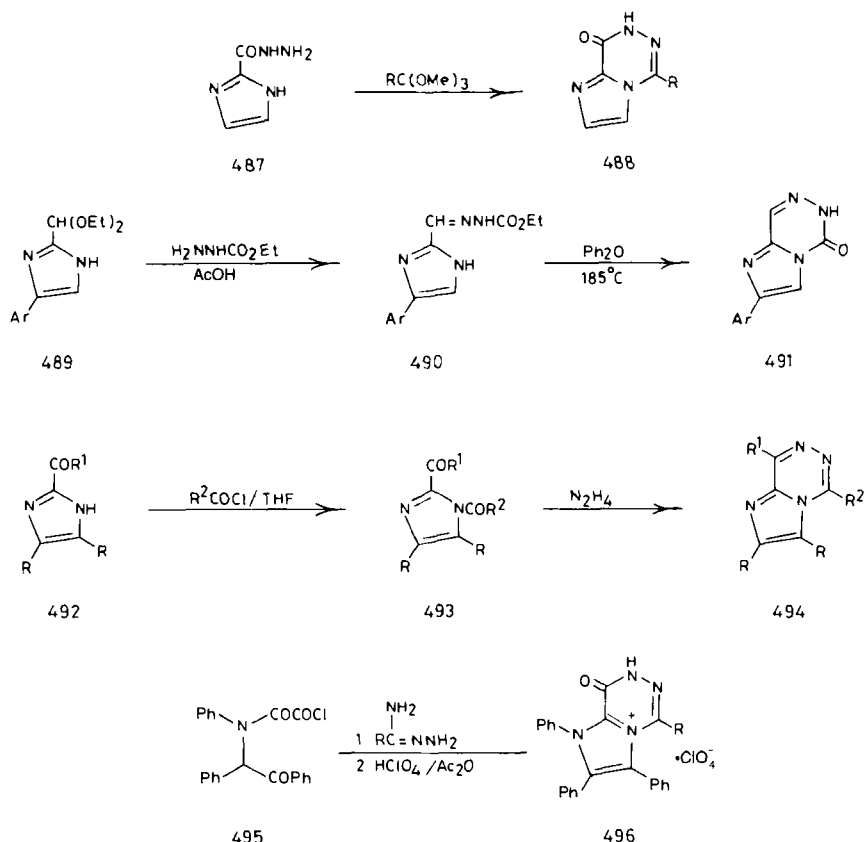
Acylation of 2-arylimidazoles **492** gave 1-acyl-4,5-disubstituted imidazoles **493**, whose cyclocondensation with hydrazine hydrate gave (88JIC784) imidazotriazines **494**.

Sequential treatment of oxamoyl chloride **495** with imidrazones and then with perchloric acid and acetic anhydride gave **496** (86S635) (Scheme 103).

5. *Imidazo[1,5-d][1,2,4]triazines*

Imidazotriazines **499** were formed (78USP4107307, 78USP4107308; 79JHC277; 83EUP85756, 83USP4395547) by the thermal cyclization of hydrazonoimidazole derivatives **498**. Methylation of **499** gave **500**, whose reaction with amines gave **501**. Reaction of **497** with dimethyl thiosemicarbazide gave **502**. They showed antihypertensive activity and inhibited cyclic AMP phosphodiesterase and served as useful antiasthmatic agents. They also are used as herbicides and completely control weed growth (78GEP2804435; 79USP4168964) (Scheme 104).

Imidazo[1,5-d][1,2,4]triazin-1(2*H*)-ones **504** were prepared (78-USP4115572; 79JHC277; 88USP4743586) by the cyclization of hydrazide **503** with triethyl orthoesters. 1,2,3,4-Tetrahydro-2,4,4-trimethyl-8-nitroimidazo[1,5-d][1,2,4]triazin-1-one **506** was isolated as a byproduct during the course of purification of hydrazide **505**, whose structure was determined (91MI4) by crystal structure analysis. They had antiasthmatic

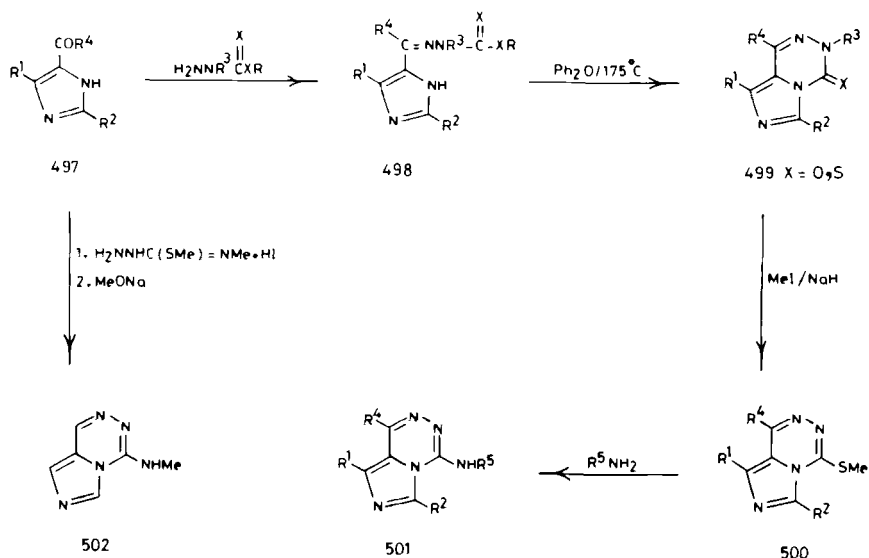


SCHEME 103

activity in the positive cutaneous anaphylaxis test and lowered arterial pressure in spontaneously hypertensive rats (Scheme 105).

6. Imidazo[4,5-*e*][1,2,4]triazines

The imidazo[4,5-*e*][1,2,4]triazines (6-azapurines) are the only examples of imidazotriazine ring systems that do not have a bridgehead nitrogen. Their synthesis could be achieved by the use of reagents for one carbon atom insertion with ortho-diamines of a triazine ring. Thus, benzaldehyde, triethyl orthoformate (76CPB2274; 90LA631), and triethyl orthoacetate [87JCS(P2)1455] were condensed with diamine **508** to give **509**; the former could be prepared from **507**. The crystal and molecular structure of 8,9-

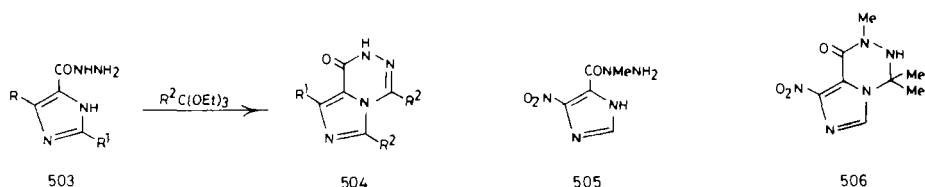


SCHEME 104

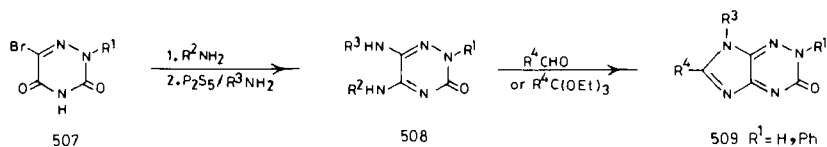
dimethyl-6-azapurin-2(1*H*)-one has been determined by single-crystal X-ray diffraction methods (87JCS(P2)1455] (Scheme 106).

Treatment of 6-arylidenehydrazino-3-alkyl-5-nitrouacils **510** with ethanolic KOH caused a benzylic acid type of rearrangement to give **511**, which were alkylated to give **512**, whose cyclization with diethyl azodicarboxylate gave (80H1295) **513** by intramolecular cycloaddition through valence isomerization and then aromatization with diethyl azodicarboxylate (Scheme 107).

Treatment of the derivatives of 7-azalumazines, **514**, with alcoholic sodium hydroxide caused a benzilic acid type of rearrangement via **515**, followed by decarboxylation and oxidation by air or potassium permanga-



SCHEME 105

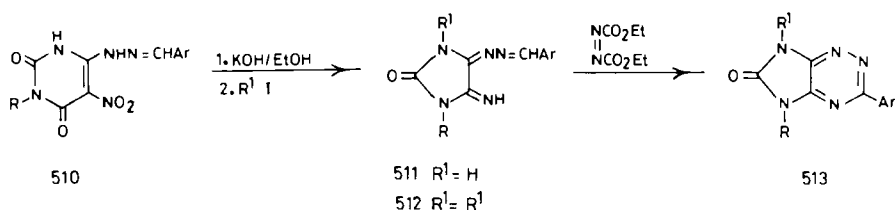


SCHEME 106

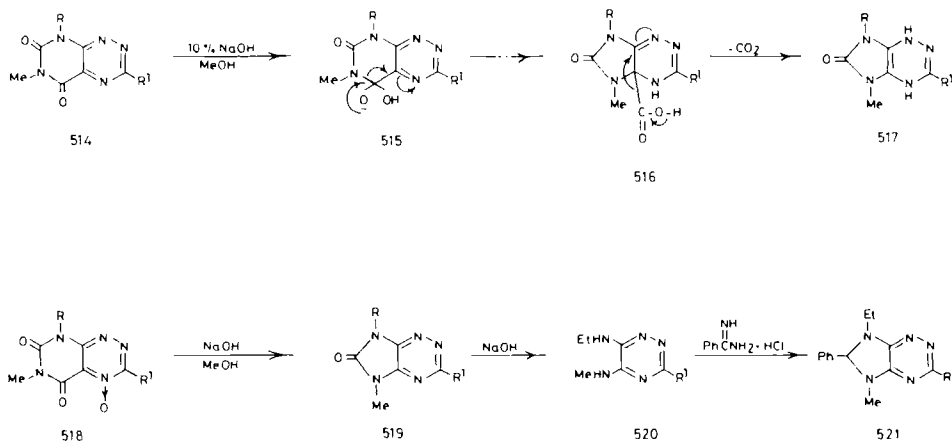
nate to give 5*H*-imidazo[4,5-*e*][1,2,4]triazin-6(7*H*)-ones (6-azapurines) **519** (76H1503; 78CPB3154; 80JHC869; 85KGS277; 87KGS1252; 87MI9). Prolonged treatment of **519** with alcoholic alkali caused ring cleavage to give **520**, which were treated with $\text{Ph}(\text{C}=\text{NH})\text{NH}_2\text{HCl}$ to give **521**. Ring cleavage of reumycin **514** ($R = R' = \text{H}$) and fervenulin **514** ($R' = \text{H}$, $R = \text{Me}$) with alkali at pH 12 opened the ring at the first stage, which was cyclized at pH > 13 to give **517**, via **516**, which could be oxidized with potassium permanganate to give **519** (85KGS277; 87KGS1555, 87MI3). Deoxygenation of the *N*-oxide group and ring contraction of the pyrimidine moiety of **518** by the action of alkali gave **519** (76CC658; 78JOC464). The reaction was successfully carried out with oxides of fervenulin and toxoflavin (Scheme 108).

Ring contraction was also achieved by the action of methanolic alkali or by acetic anhydride on amino derivatives **522** to give **523** and **524**, respectively (76CC658). Imidazotriazine **526** was obtained (86M11) from the reaction of xanthricin **525** with aqueous solutions of amines. Treating fervenulin with potassium amide in liquid ammonia containing potassium permanganate gave the respective imidazotriazinone (88KGS1696) (Scheme 109).

Formation constants of Ag(I) complexes with 5,7-dimethyl-4*a*,7*a*-diphenyloctahydroimidazo[4,5-*e*][triazin-6-one-3-thione was determined potentiometrically (79MI2).



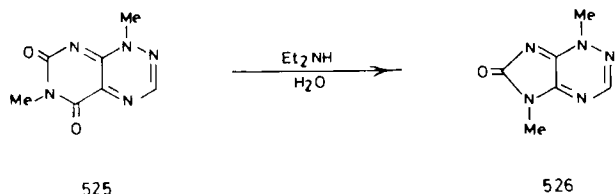
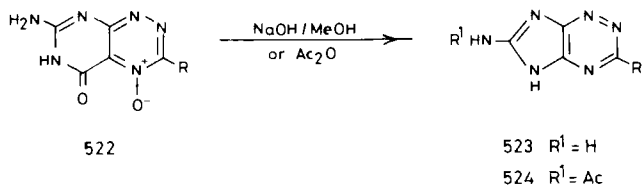
SCHEME 107



SCHEME 108

7. Imidazo[5,1-f][1,2,4]triazines

This ring system may be prepared from **527** by condensation with amidrazone or aminoguanidine derivatives to afford **528**, which on reaction with polyphosphoric acid gave imidazo[5,1-f][1,2,4]triazin-4(2*H*)one **529**



SCHEME 109

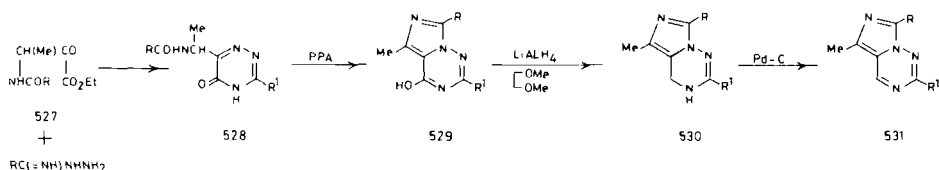
[78GEP2811780; 79JCS(P1)1120; 80EUP9384; 80JCS(P1)1139]. Reduction of the carbonyl function of **529** to provide **530** was best achieved with lithium aluminium hydride in 1,2-dimethoxyethane. Dehydrogenation of **530** over palladium on charcoal afforded **531**. They were prepared for use as muscle relaxants and bronchodilators (Scheme 110).

Treatment of **532** with hydrazine gave hydrazide **533**, which underwent a Curtius rearrangement to give **534** via an isocyanate intermediate. On the other hand, benzylation of **532** gave **535**, which reacted with hydrazine to give **536**. Reaction of the latter with sodium nitrite in hydrochloric acid gave **537**, which on acylation afforded **538**, which in turn was converted to imidazo[5,1-*f*][1,2,4]triazine **539** by heating with phosphorus oxychloride. In an alternate process, amide **538** was catalytically debenzylated and the product cyclized with polyphosphoric acid to give **539**, whose reduction with lithium aluminium hydride followed by catalytic dehydrogenation gave **542**. Reaction of **539** with methanesulfonyl chloride in acetic acid gave **540**, which reacted with LiAlH_4 -THF, followed by dehydrogenation to give **541**. Compound **542** is susceptible to nucleophilic addition at the 3,4-azomethine bond; thus with methylmagnesium bromide, dimedone, or sulfur dioxide, it gave adducts **543**. Reaction of **542** with nitrous acid gave **544** [79JCS(P1)1120] (Scheme 111).

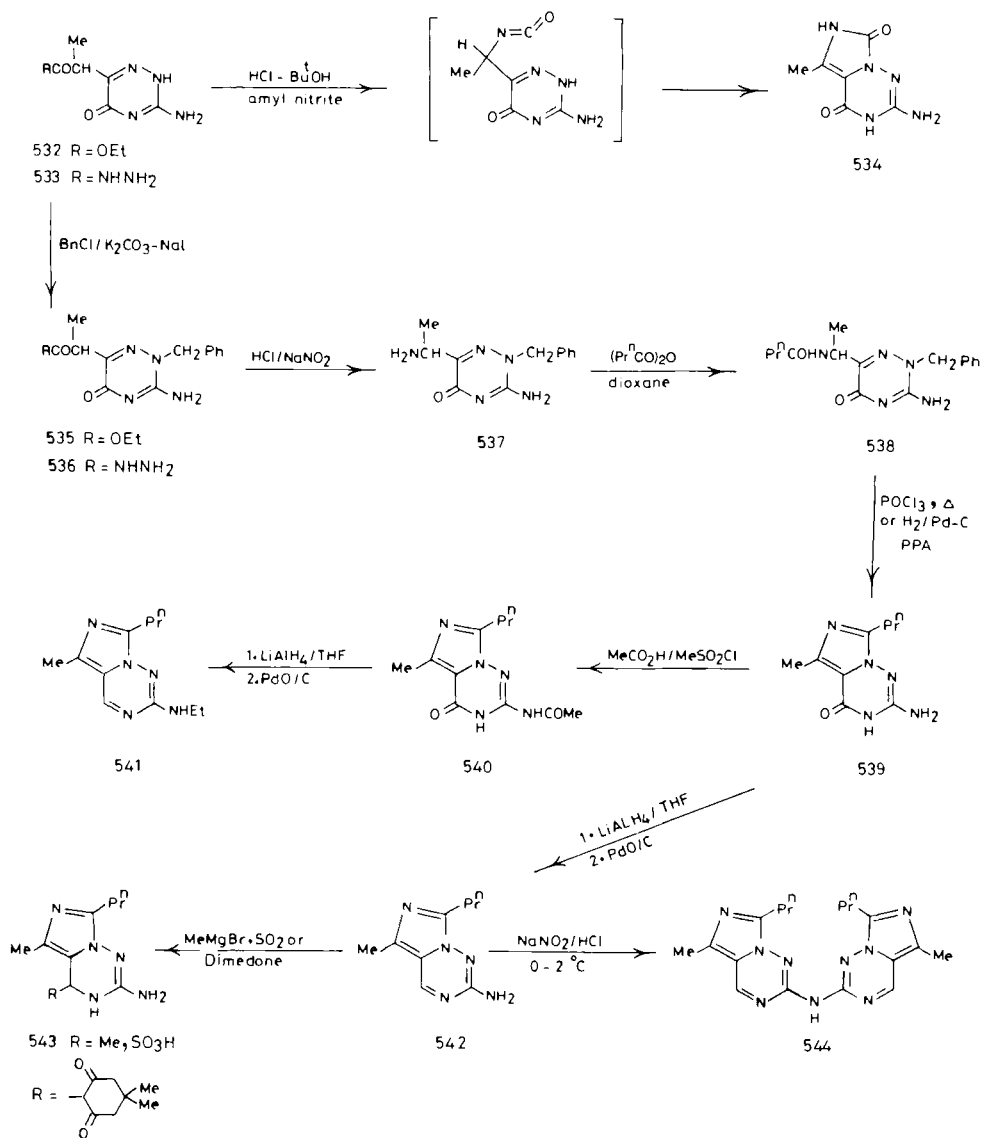
Novel isosteres **545** of the antiviral agent acyclovir were synthesized in three stages (84JHC697) by dehydrative coupling of 3-amino-6-aminomethyl[1,2,4]triazin-5-(4*H*)-one with 2-(benzoyloxy)ethoxyacetic acid to give the respective amide that cyclized and deprotected to give **545**. It showed no activity against herpes simplex virus types I and II in cell culture (Scheme 112).

[(Triphenylphosphoranylideneamino)-arylidineamino]imidazoles **546** with alkyl or arylisocyanates gave (89S843) imidazo[5,1-*f*][1,2,4]triazines **547** (Scheme 113).

Triazinoimidazobenzodiazepine **551** was obtained (80JHC1697) by heating **550** in acetic acid. The latter was prepared from **548** by the action of ammonia to give **549**, whose reaction with triethylorthoacetate gave **550** (Scheme 114).



SCHEME 110



SCHEME 111



SCHEME 112

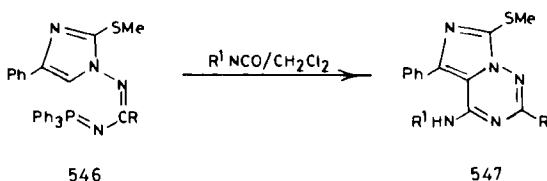
The site of protonation of the 2-aminoimidazo[5,1-*f*]triazine system was studied by X-ray, ^{13}C -NMR, and CNDO/2 [79JCS(P2)1327] and it was found to be N-6.

D. [1,2,4]TRIAZINO[*x,y-z*]BENZIMIDAZOLES

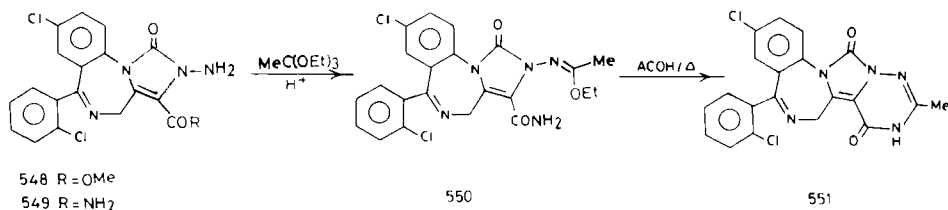
The number of possible triazinobenzimidazoles is less than that for imidazolotriazines when fusion of the triazine ring takes place on the imidazole ring. It should be noted that *z* in imidazotriazines indicates the edge of the triazine ring, whereas in the triazinobenzimidazoles it indicates the edge of the benzimidazoles.

1. [1,2,4]Triazino[2,3-*a*]benzimidazoles

This ring system could be prepared by building either of the two heterocycles and then doing an annulation. Thus, cyclization of ethyl *o*-nitrophenylhydrazonocynoacetyl carbamate **552** afforded **553**. Reduction of **553** by the action of iron(II) sulfate gave **554**, which on acid hydrolysis gave **558**. Cyclization of *o*-aminophenyl derivatives **554** and **558** to **555** and **559**, respectively, was effected (77CCC894) by treatment with acid. Phthalimido derivatives of **554** could also be cyclized to this



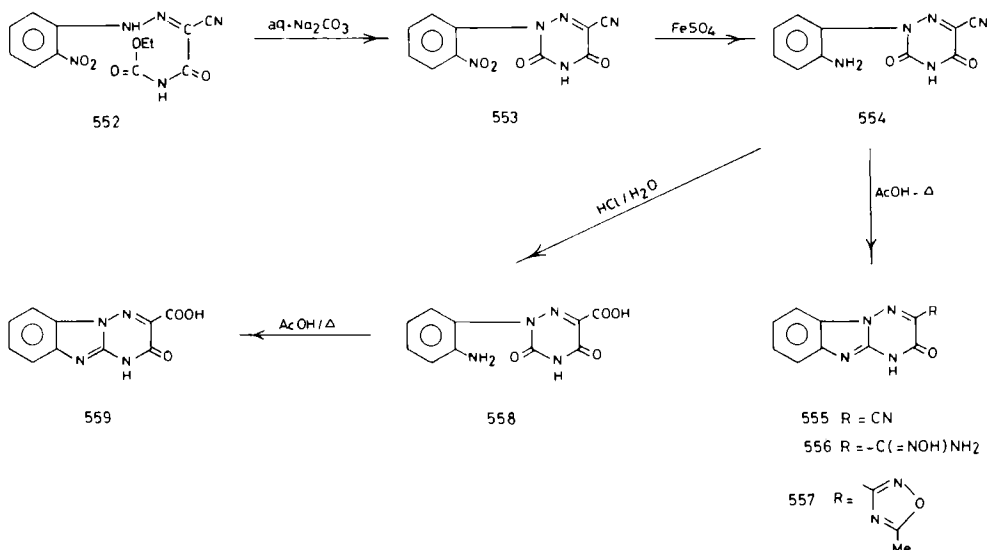
SCHEME 113



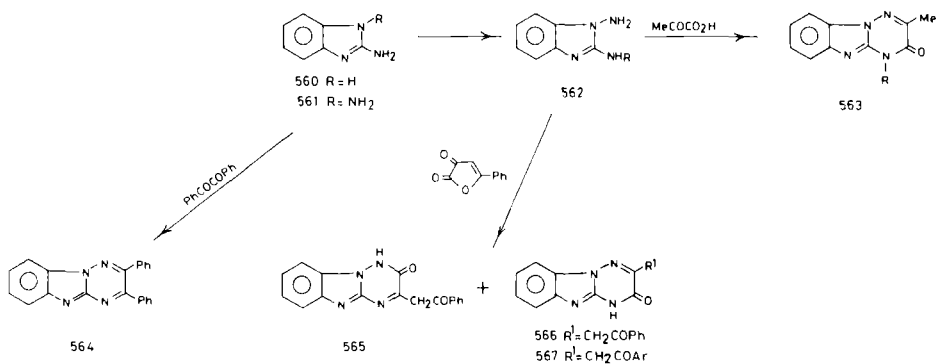
SCHEME 114

ring system. The nitrile group in **555** could be transformed to amidooxime **556** and oxadiazole **557** (77CCC894) (Scheme 115).

1,2-Diaminobenzimidazoles **561** were used frequently as a source of this ring system; they were synthesized by the cyclization of *o*-acylhydrazidoanilines with cyanogen bromide or by the amination of **560**. Its reaction with benzil provided **564** (77JOC542). Triazinones **563** and the *N*-substituted derivative of **567** were prepared by the condensation of **562** with pyruvic acid (88KGS1070) and aroylpyruvic acid (85KGS1402), respectively. The tautomerism of **563** was studied (92KGS937). The cyclocondensation of **561** with 5-phenyl-2,3-dihydro-2,3-furandione gave (87KGS533) a mixture of triazinobenzimidazoles **565** and **566** (Scheme 116).



SCHEME 115

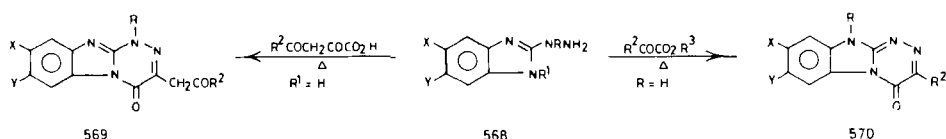


SCHEME 116

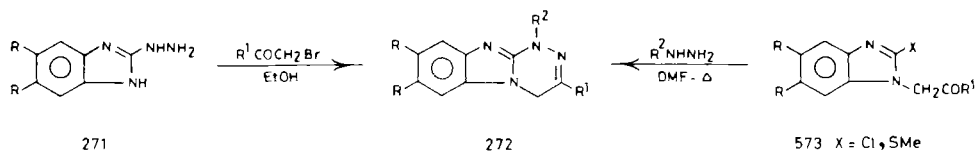
2. [1,2,4]Triazino[4,3-a]benzimidazoles

Hydrazine derivatives **568** are excellent precursors of this ring system. Treatment of hydrazinobenzimidazoles **568** ($R^1 = H$) with aroyloxopropionic acids in the presence of acetic acid afforded (76URP502888; 77UKZ746; 90UKZ1089) triazinobenzimidazoles **569**. The naphthylene analogue of **569** was prepared in a similar manner (76URP502888). Triazinobenzimidazoles **570** were obtained [89IJC(B)698] by reaction of 2-hydrazinobenzimidazoles **568** ($R = H$) with ethyl pyruvate in a neutral medium, followed by hydrolysis and cyclization. Two tautomeric forms exist for **570** ($R = H$) due to the labile hydrogen. The compounds displayed antibacterial and antifungal activities [89IJC(B)698] (Scheme 117).

Cyclization of hydrazine **571** to **572** was achieved (76KGS715, 76MI3) by reaction with phenacyl bromide. Alternatively, the reaction of phenacyl bromide with a benzimidazole having a leaving group at the 2-position of the imidazole ring gave **573**, whose reaction with hydrazines gave **572** (74KGS1696; 75KGS1287, 75MI1, 75MI2; 76KGS1424). The naphthylene analogues were prepared in a similar manner (74KGS1696; 76MI3, 76UKZ64) (Scheme 118).



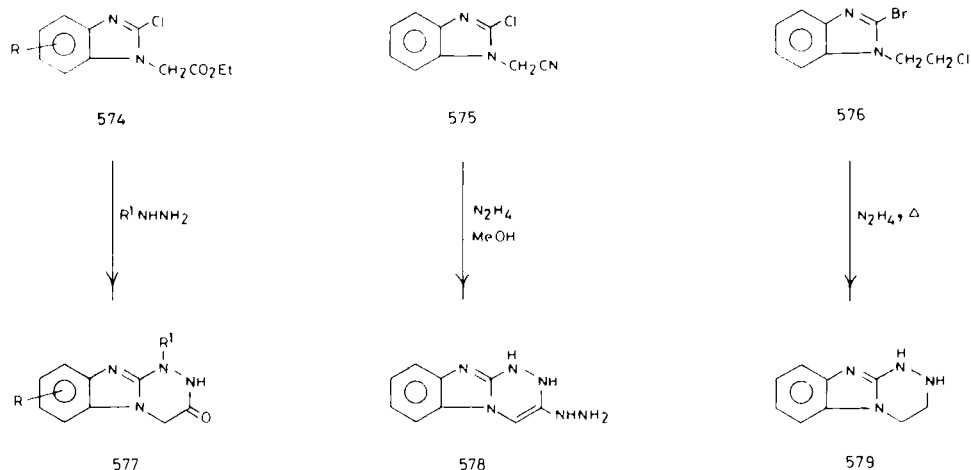
SCHEME 117



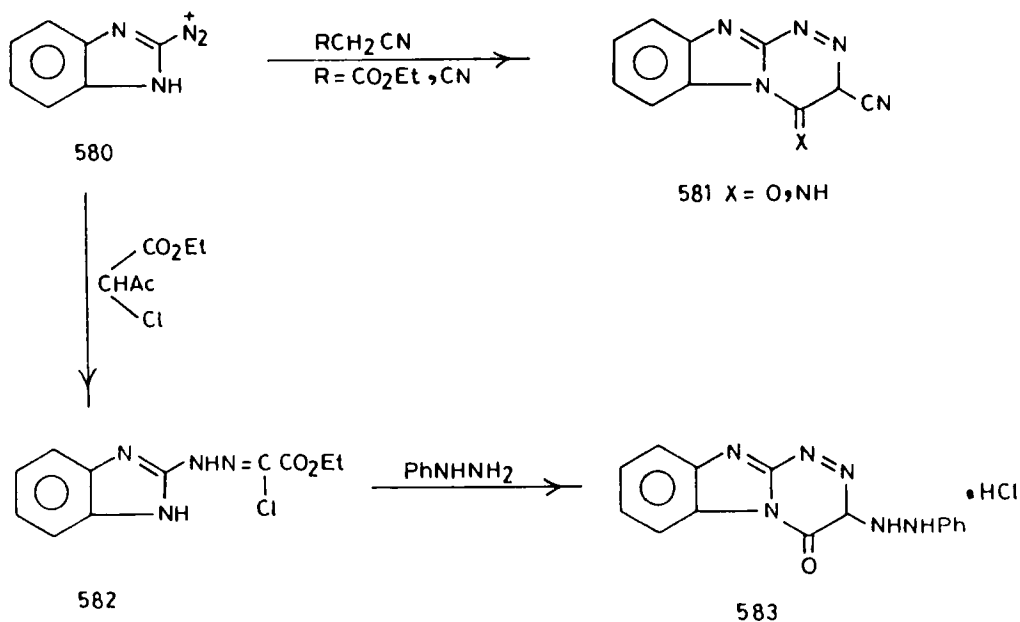
SCHEME 118

The above reactions were extended to ethoxycarbonylmethyl derivatives **574**, whereby the triazinone **577** could be prepared (87M17). These compounds were tested for antiparasitic activity against *Trichomonas vaginalis*, *Entamoeba histolytica*, *Hymenolepis arna*, and *Nippostrongylus brasiliensis* (87M17). Triazinobenzimidazole **578** was prepared by the alkylation of 2-chlorobenzimidazole with chloroacetonitrile to give **575**, followed by reaction with hydrazine [87SC1533; 88CI(L)785]. The partially saturated derivative **579** and its naphtho analogue were prepared (75KGS422) by the reaction of hydrazine with **576** and its naphtho analogue, respectively (Scheme 119).

The synthesis of this ring system was also carried out by coupling of 2-diazoimidazole **580** with the activated nitrile ethyl cyanoacetate to give **581** (82M13). Its coupling with ethyl α -chloro acetoacetate gave **582**, which cyclized (83M12) by the action of phenylhydrazine to give **583** (Scheme 120).



SCHEME 119



SCHEME 120

3. [1,2,4]Triazino[4,5-a]benzimidazoles

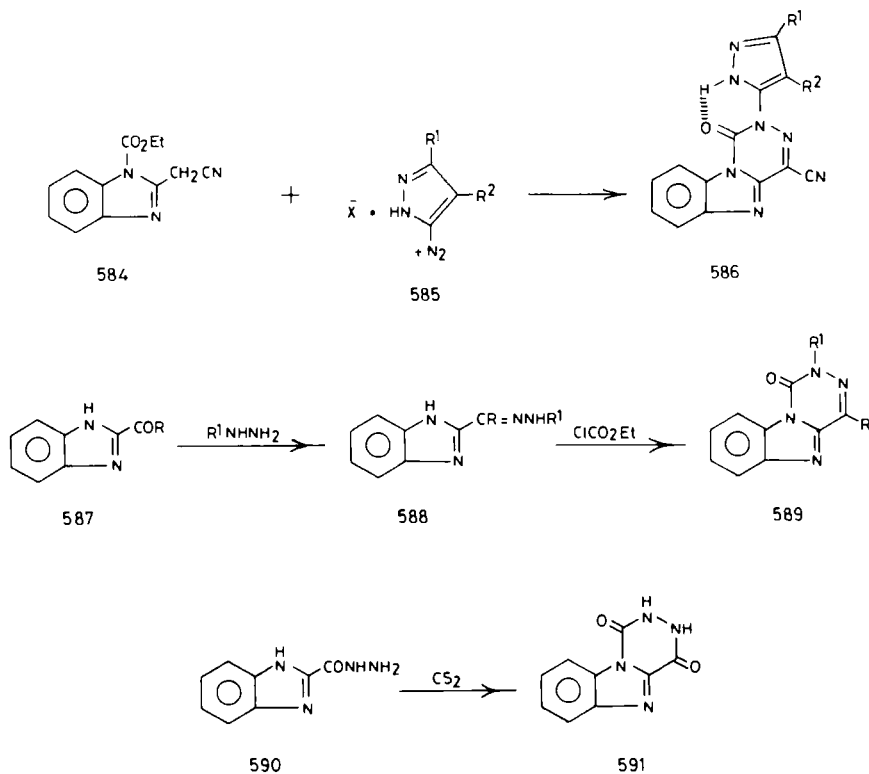
Coupling of 2-(1-ethoxycarbonylbenzimidazol-2-yl)acetonitrile **584** with diazonium salt **585** gave (84CCC275) **586** without the isolation of the respective hydrazone. Alkaline hydrolysis of the respective 2-aryl analogue of **586** caused opening of the triazinone ring (74MI1).

Treatment of 2-acetyl- or 2-formyl-benzimidazole **587** with hydrazines gave the corresponding hydrazones **588**, which cyclized with ethyl chloroformate to give [84JCR(S)384] triazinobenzimidazoles **589**.

Reaction of benzimidazole-2-carboxylic acid hydrazide **590** with carbon disulfide gave triazine **591** (86JPR515) (Scheme 121).

4. [1,2,4]Triazino[1,6-a]benzimidazoles

The reported examples of ring system **593** were prepared by heating 1-amino-3-alkylbenzimidazolium iodides **592** with aromatic aldehydes in polar aprotic solvents to give **593** via intermediate Schiff bases (86KGS346) (Scheme 122).

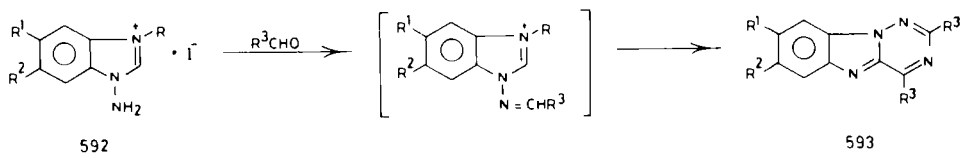


SCHEME 121

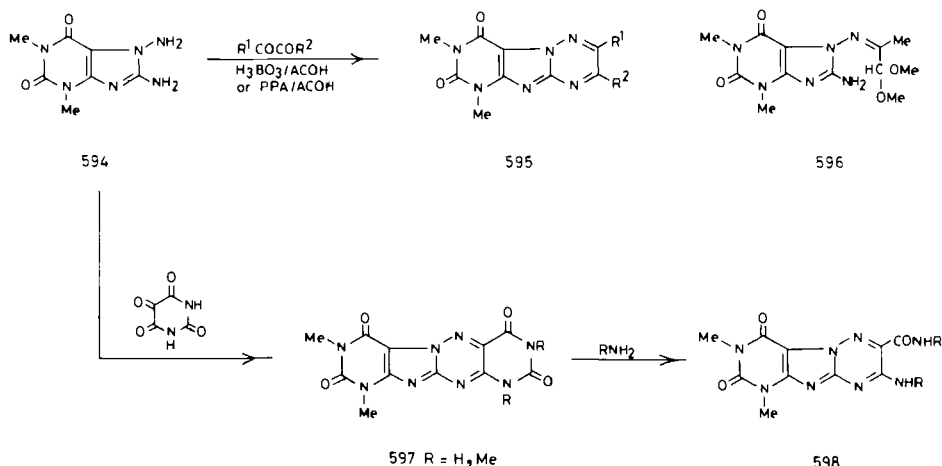
E. [1,2,4]TRIAZINO[x,y-z]PURINES

1. [1,2,4]Triazino[2,3-f]purines

[1,2,4]Triazino[2,3-f]purines **595** were prepared by treatment of 7,8-diamino-1,3-dimethylxanthine **594** with dicarbonyl compounds such as



SCHEME 122



SCHEME 123

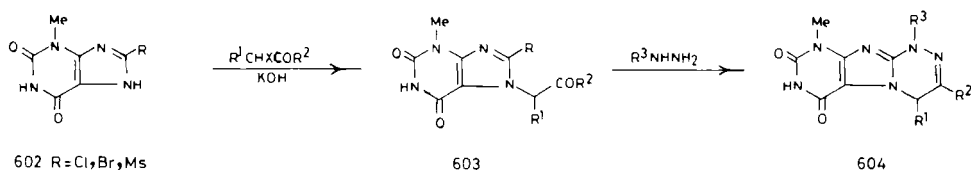
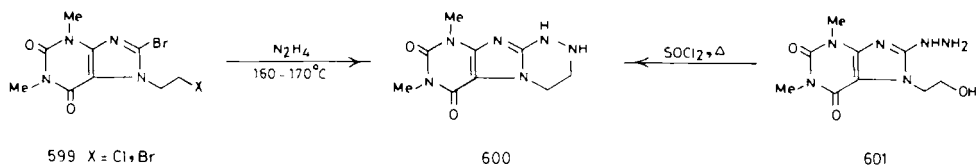
glyoxal, diacetyl, dibenzoyl, pyruvaldehyde dimethylacetal, phenylglyoxal, and others (87KGS1398; 88JHC791, 88UKZ531). Intermediate **596** could be isolated and cyclized to the respective derivative **595** (88JHC791). The spectral luminescent properties of **595** were determined (88UKZ531). The respective 1,8-naphthylene was also prepared (87KGS1398; 88UKZ531).

Condensation of **594** with alloxan followed by methylation of the presumably formed purino[7,8-*g*]-6-azapteridine gave **597**. Treatment of the latter with alkylamines afforded (87CPB4031) [1,2,4]triazino[2,3-*f*]purines **598**. Compound **597** was active against P388 leukemia. Vascular relaxing effects of **598** were determined, but none showed potent activity (87CPB4031) (Scheme 123).

2. [1,2,4]Triazino[3,4-*f*]purines

Triazinopurines **600** were obtained by cyclization of **599** with hydrazine or by cyclization of **601** with thionyl chloride (75MI6).

Phenacyl derivatives **603**, having a leaving group at 8-position, were used as precursors for the synthesis of ring system **604** by their reactions with hydrazines (74KGS1696; 75MI5; 81MI3; 86KFZ187, 86KFZ427). Acyl derivatives **603** were prepared by treatment of **602** with potassium hydroxide to give the potassium salt, which was acylated with α -haloketones. Reaction of **604** with phosphorus pentasulfide gave the 6-thio analogue of **604** (81MI3), which reacted with morpholine or piperidine and



SCHEME 124

formaldehyde in a Mannich reaction (86KFZ187). The pharmacological properties of various derivatives of **604** have been evaluated (86KFZ427). Triazinoxanthine **604** ($R^1 = H$, $R^2 = Me$, $R^3 = Et$) prolonged ethaminal sleep in white rats (86KFZ187) (Scheme 124).

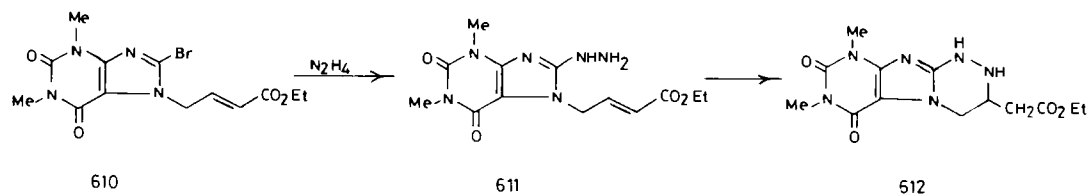
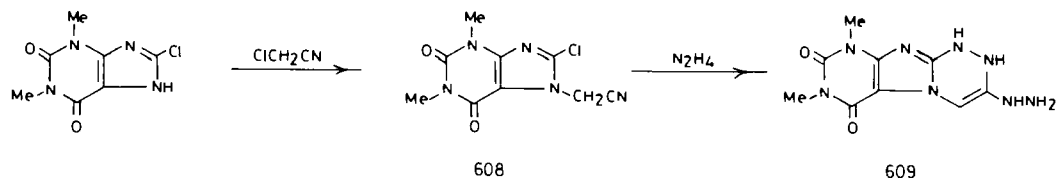
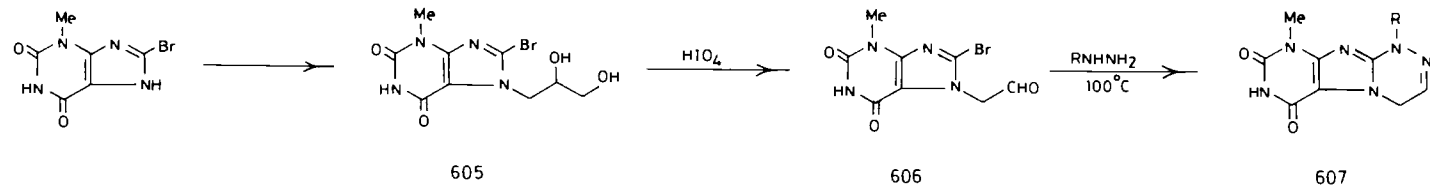
The generation of a suitable group for cyclization onto the nitrogen atom of **602** was achieved by the addition of glycidol to xanthine to give **605**, whose oxidation by periodic acid gave aldehyde **606**. This aldehyde cyclocondensed with hydrazine on heating to give triazinopurines **607** but at lower temperature the hydrazone of **606** was formed (85M12).

Alkylation of chlorotheophylline with chloroacetonitrile gave **608** and cyclization with hydrazine gave [88CI(L)785] triazine derivative **609**. Condensation of the latter with different aldehydes gave the corresponding hydrazones.

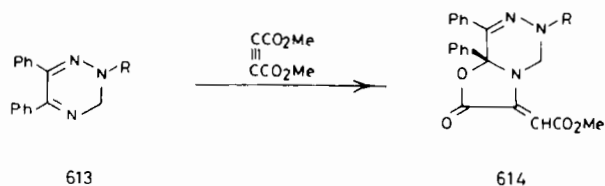
Triazinopurinyl derivative **612** was prepared (91S625) by hydrazinolysis of **610**, followed by cyclization of the presumably formed hydrazine derivative **611** (Scheme 125).

VIII. Oxazolo[1,2,4]triazines

There are three isomeric ring systems reported during the period covered by this review.



SCHEME 125



SCHEME 126

OXAZOLO[x,y-z][1,2,4]TRIAZINES

1. Oxazolo[3,2-d][1,2,4]triazines

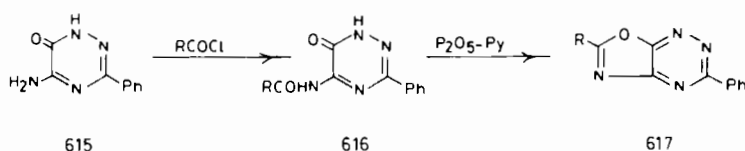
Examples of this ring system were synthesized by nucleophilic addition of **613** to dimethyl acetylenedicarboxylate in moist solvents to afford the ylidene-substituted oxazolo[3,2-d][1,2,4]triazine **614**. Its X-ray crystal structure has been described [90JCR(S)354] (Scheme 126).

2. Oxazolo[4,5-e][1,2,4]triazines

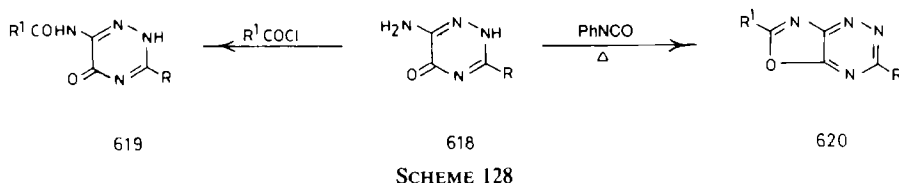
The representatives of this heterocyclic system were prepared by cyclodehydration of 5-acylamino-6-ones **616**, obtained from **615**, with phosphorus pentoxide to give the corresponding 3-phenyloxazolo[4,5-e]triazines **617** (87AJC977) (Scheme 127).

3. Oxazolo[5,4-e][1,2,4]triazines

Derivatives of oxazolo[5,4-e][1,2,4]triazines **620** were prepared (87AJC977) by cyclodehydration of the respective 6-acylamino-5-ones **619**, obtained by acylating **618**, with phosphorus oxychloride or phosphorus pentoxide. 6-Phenyloxazotriazines **620** ($\text{R}^1 = \text{Ph}$) were also obtained directly when aminotriazinones **618** were heated with benzoic acid anhydride. By a different route, 6-aminotriazin-5-one **618** was con-



SCHEME 127



verted to 6-anilino derivative **620** ($R^1 = \text{NHPh}$) by the action of phenyl isocyanate in dimethylformamide, but it is not a successful route to this ring system (Scheme 128).

IX. Thiazolo[1,2,4]triazines

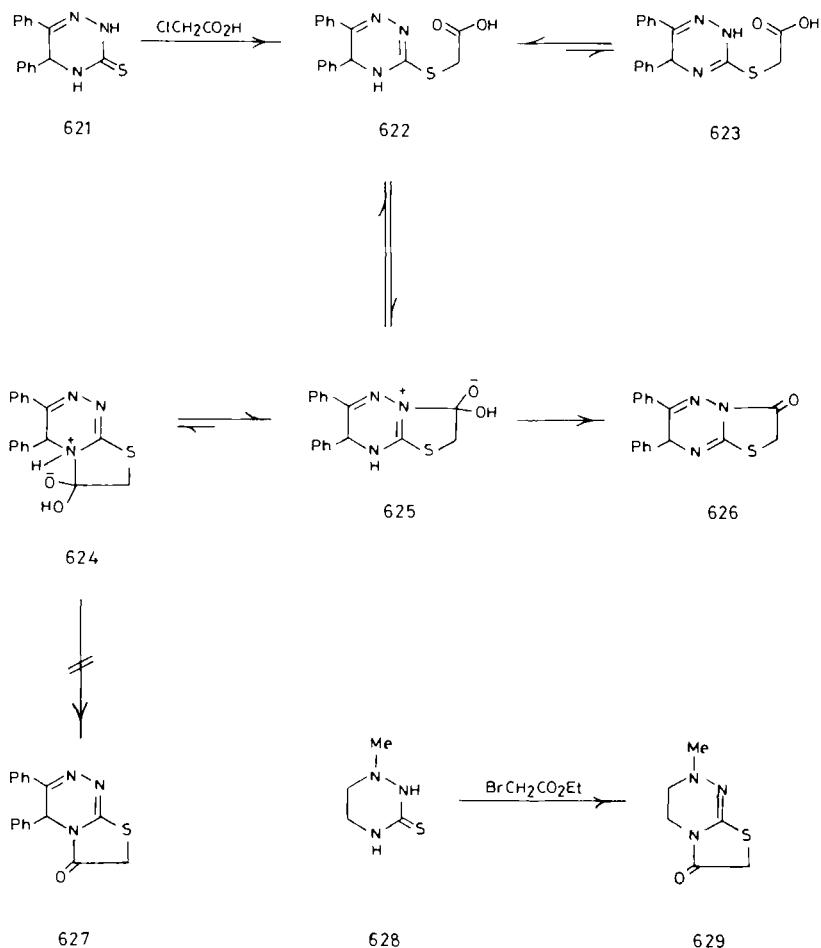
A. THIAZOLO[x,y-z][1,2,4]-TRIAZINES

There are 10 thiazolo and 8 isothiazolo isomeric possible structures. However, the only reported examples are 6 of the former and 1 of the latter.

1. Thiazolo[3,2-b][1,2,4]triazines

The site of cyclization of the reaction product of **621** with chloroacetic acid was reported (75IJC109) to give thiazolo[2,3-c][1,2,4]triazine **627**, based on earlier studies. However, thiazolo[3,2-b][1,2,4]triazine structure **626** [77IJC(B)46] was then given to that product. The argument for the formation of **626** rather than **627** was that the initially formed intermediate **622** would possess a greater amount of resonance energy gained by the delocalization of the lone pair of electrons over a larger segment of the molecule. The N-2 site in **622** has pyridine-like sp^2 character, which renders it more nucleophilic than N-4, which has pyrrole-like sp^3 character. Hence, N-2 will attack the carbonyl carbon of the acid giving **625**, which on prototropic change and subsequent loss of a molecule of water gives **626**. On the other hand, formation of thiazolo[2,3-c][1,2,4]triazine analogues **629** from other derivatives **628** in earlier studies (71JHC621) is still acceptable (Scheme 129).

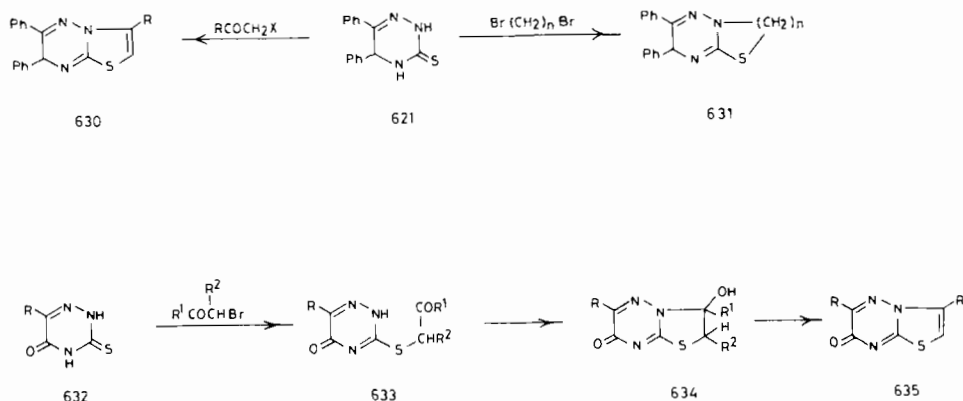
Reaction of **621** with α -haloketones gave [77IJC(B)46] [3,2-b] isomers **630** rather than the earlier reported [2,3-c] isomers. The reaction of **621** with 1,2-dibromoethane and 1,3-dibromopropane gave **631**. Ring-chain tautomerism in 3-hydroxythiazolo[3,2-b][1,2,4]triazin-7-ones **634** has been studied (77CB1492). The hydroxyl groups of the most stable conformer



SCHEME 129

were deduced through an NMR study to be axial (77CB1492). Thiazolo derivatives **635** were prepared as anti-inflammatory agents (79PHA392; 88EUP276805) (Scheme 130).

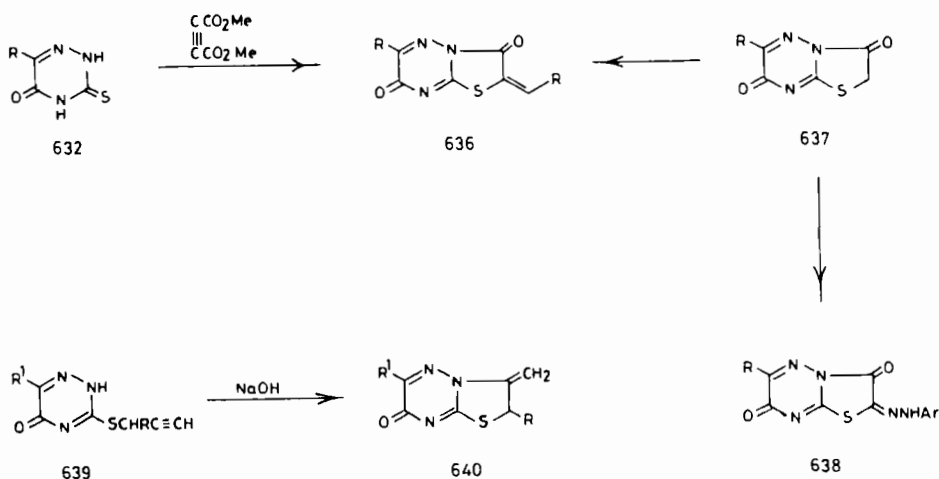
Thiazolotriazines **636** (R=CO₂Me) were prepared [84JCS(P1)2707] by cycloaddition of dimethyl acetylenedicarboxylate with triazine derivative **632**. Derivatives of thiazolo[3,2-*b*][1,2,4]triazin-3,7-diones **637** have been formed (74JPR163) on reaction with aromatic aldehydes and diazonium salts to give **636** (R = Ar) and **638**, respectively. Regioselective catalyzed



SCHEME 130

cyclization (84H1225; 85TL1237) of 3-propargylthio[1,2,4]triazin-5(2H)-ones **639** by sodium hydroxide gave **640** (Scheme 131).

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7*H*-triazolo[3,2-*b*][1,2,4]triazin-7-one (HWA-131) is a non-immunosuppressive drug that effectively inhibited carrageenan-induced paw edema, attenuated the active Arthus reaction, and demonstrated antierythema as well as antipyretic activity. Part of the antiinflammatory effect of this new compound is most probably related to its antioxidative activity as well as inhibition of lipoxigenase

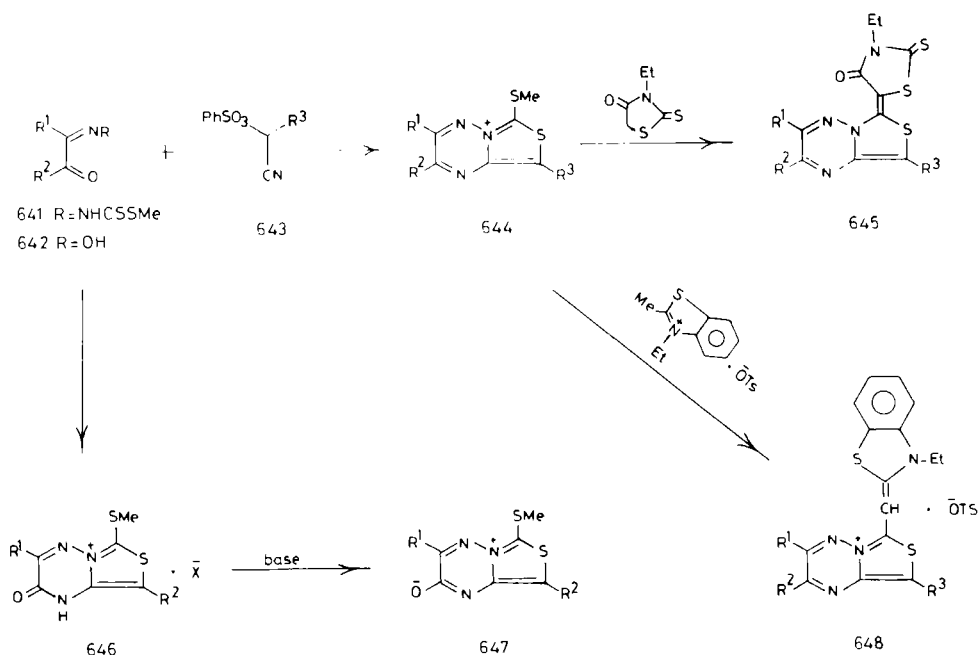


SCHEME 131

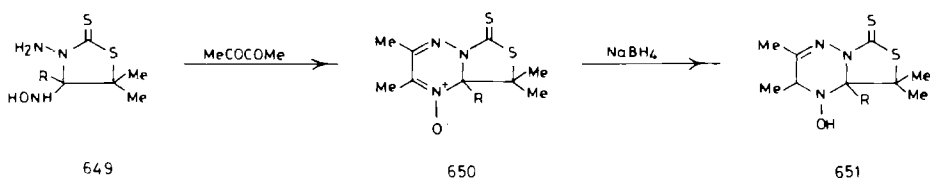
metabolites. It is an effective nonsteroidal anti-inflammatory agent with immunomodulating properties that combat human autoimmune disorders (89MI4).

2. *Thiazolo[3,4-b][1,2,4]triazines*

Thiazolo[3,4-*b*][1,2,4]triazinium salts **644** were prepared (85KGS498; 85URP1075676) by condensation of cyanoalkyl sulfonic ester **643** with **641** and **642**. Similarly, cyclization of the hydrazones **641**, obtained from α -oxo acids, with nitriles gave (85KGS1497) **646**, which tautomerize to mesoionic structure **647** when treated with base. Reaction of perchlorate **644** with 3-ethylrhodamine or 2-methyl-3-ethylbenzothiazolium tosylate gave **645** and **648**, respectively (86KGS1693). Similarly, the reactions of **646** gave monomethine and null-methine dyes (88KGS848). Various symmetric and asymmetric thiazolotriazine cyanine dyes were prepared. Quantum chemical calculations provide (88KGS418) electron density distributions. Absorption spectra were studied (89ZOR597) (Scheme 132).



SCHEME 132



SCHEME 133

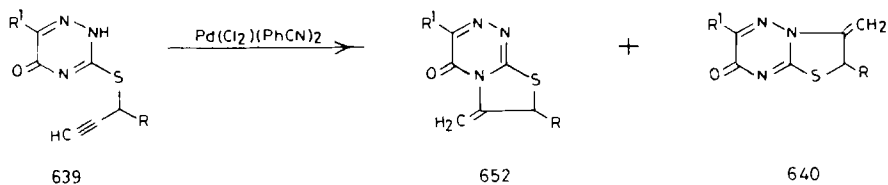
Cyclocondensation of 3-amino-4-(hydroxyamino)thiazolidine-2-thiones **649**, with diacetyl gave **650**, which were reduced by sodium borohydride to give the corresponding *N*-hydroxy derivatives **651** (87KGS554) (Scheme 133).

3. *Thiazolo[2,3-*c*][1,2,4]triazines*

This ring system may be approached by building a triazine ring followed by constructing the thiazole ring or vice versa. Most of the methods used in the period of the review belong to the second approach. The selective formation of **652** from **639** was achieved (85TL1237) by catalysis with a palladium(II) salt. Generally the reaction provides **652** as a main product together with small amounts of **640** and the depropargylated product of **639**. The isomeric [3,2-*b*] was prepared exclusively from **639** by the action of sodium hydroxide. This showed the efficiency of the method for preparing the two isomeric compounds by selecting the reaction conditions. The reaction was suggested to proceed by attack of N-4 or N-2 on the acetylenic triple bond activated by coordination with palladium(II). The difference in the reaction pathway from that of a Pd-catalyzed S→N allylic rearrangement of 3-allylthio[1,2,4]triazin-5(2*H*)-ones may be due to the high reactivity of acetylenes toward nucleophiles and also to an unsuitable conformation of **639** for a [3,3]sigmatropic rearrangement (Scheme 134).

Reaction of **653** with phenacyl bromide gave **654** (79PHA392). The benzotriazine analogue of **654** was similarly prepared (80H149). The difference in the sequential formation of the two heterocycles could lead to different isomeric products, as shown by constructing the thiazole ring on **655** by phenacyl bromides to give **656**, whose cyclization gave **657**. The reverse situation was shown previously for the synthesis of the [3,2-*b*] analogue from **632**.

Thiazolo[2,3-*c*][1,2,4]triazines **658** were prepared (84LA1302) regio-specifically by cyclizing 2-hydrazono-2-thiazoline **659** with glyoxylic acid or ester. They had herbicidal activity. Condensation of **659** with oxamic acid ethyl ester gave hydrazide **660**, which was cyclized with sodium

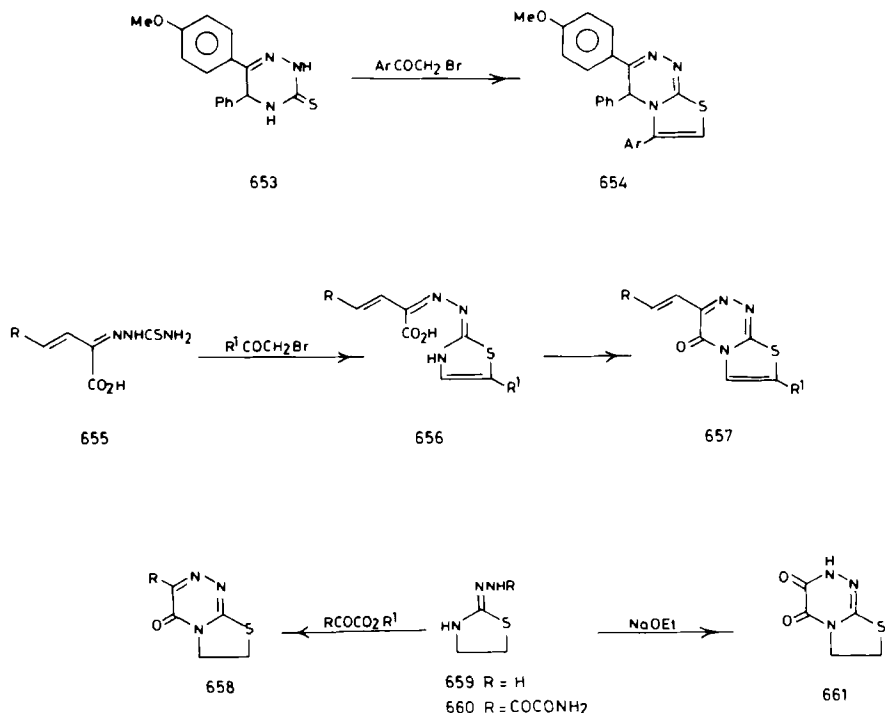


SCHEME 134

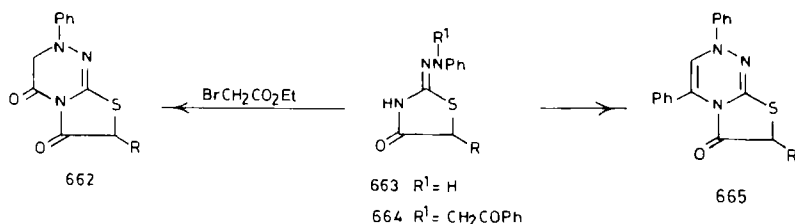
ethoxide to give **661**. Cyclocondensation of **659** with diethyl oxalate led directly to **661** (81CB1200) (Scheme 135).

Treatment of phenylhydrazonothiazolidinone **663** with phenacyl bromide gave **664**, which was cyclized [84MI2, 84ZN(B)390] to give thiazolo-triazine **665**. Cyclization of **663** with ethyl bromoacetate afforded **662** (Scheme 136).

Thiazolo[2,3-*c*][1,2,4]triazines **667** were synthesized by coupling the diazotized thiazole derivative **666** with activated nitriles to give **667** without



SCHEME 135



SCHEME 136

isolation of the respective hydrazones under a variety of coupling conditions (83JHC285; 87MI4; 90MI5; 91MI2). The reaction of **666** with dione gave ring system **668** (76M1199) (Scheme 137).

Alternatively, the thiazolotriazine ring was prepared from 1-nitro-2-aminonaphthalene with an isothiocyanate to give naphthylpyrimidine **669**, whose reaction with phenacyl bromide gave thiazoline **670**. Reduction with stannous chloride and cyclization with *N*-bromosuccinimide gave naphthothiazolotriazine **671** (74JIC631) (Scheme 138).

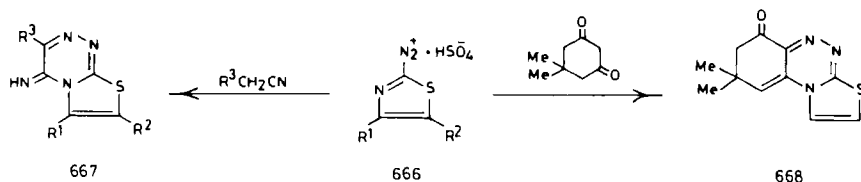
4. Thiazolo[4,3-c][1,2,4]triazines

Examples **673** and **674** were prepared by treating phenylhydrazonothiazolidinethione **672** with either ethyl bromoacetate or phenacyl bromide (86PHA101) (Scheme 139).

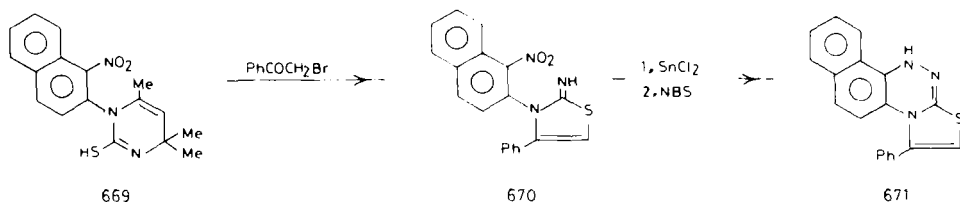
Cyclization of methyl (4*R*)-3-(2-diazo-3-oxobutanoyl)-thiazolidine-4-carboxylate (**675**) under basic conditions afforded **676** (91CC924). The reaction proceeded with retention of configuration and the structure was established by X-ray analysis (Scheme 140).

5. Thiazolo[4,5-e][1,2,4]triazines

Thiazolotriazines **678** were synthesized (87AJC693) by heating 5-acylamino[1,2,4]triazin-6(1*H*)-ones or its thio analogue **677** with phosphorus



SCHEME 137



SCHEME 138

pentasulfide in pyridine. They could also be obtained from **679** by heating with carbon disulfide or phenyl isothiocyanate (Scheme 141).

6. *Thiazolo[5,4-*e*][1,2,4]triazines*

The reaction of 6-amino[1,2,4]triazin-5(2*H*)-ones or its thione derivatives **680** with acetic anhydride gave the 6-acetamido derivatives **681** and **682**, respectively. Treatment with phosphorus pentasulfide in pyridine gave thiazolo[5,4-*e*][1,2,4]triazines **683** (84LA283; 87AJC491) (Scheme 142).

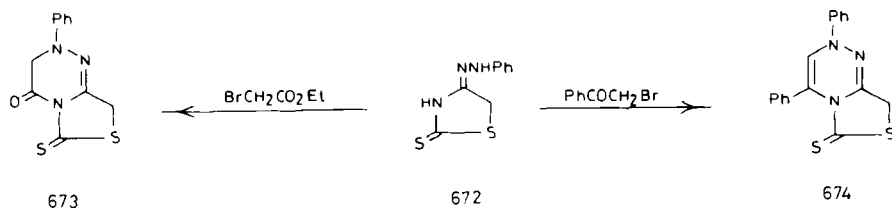
B. [1,2,4]TRIAZINO[*x,y-z*]BENZOTHIAZOLE

1. *[1,2,4]Triazino[3,2-*b*]benzothiazole*

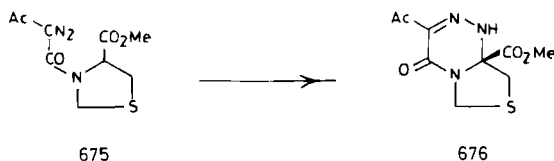
The benzo analogue **684** of [1,2,4]triazino[3,2-*b*]thiazoles was prepared (88LA1089) by heating triazine derivative **632** with 2,4-dinitrochlorobenzene or picryl chloride in *N,N*-dimethyl formamide (Scheme 143).

2. *[1,2,4]Triazino[3,4-*b*]benzothiazole*

The synthesis of 2*H*[1,2,4]triazino[3,4-*b*]benzothiazol-3(4*H*)-one **687** was achieved by condensation of 3-(carbethoxymethyl)benzothiazoline-



SCHEME 139



SCHEME 140

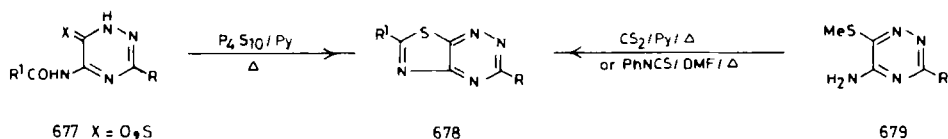
2-thione **685** ($X = S$) with hydrazine; hydrazide **686** may be formed depending on the reaction conditions (88PS71). On the other hand, condensation of **685** ($X = O$) with hydrazine gave only hydrazide **686**. Heating triazinobenzothiazole **687** with substituted benzaldehyde or acetophenone in concentrated hydrochloric acid gave thiazole derivative **688**, whereas in the presence of methanol the ester of **688** was obtained. Similarly, 5-nitrofurfural diacetate gave **688**, which exhibited bactericidal activity (80MI4; 82MI5) (Scheme 144).

C. ISOTHIAZOLO[x,y-z][1,2,4]TRIAZINES

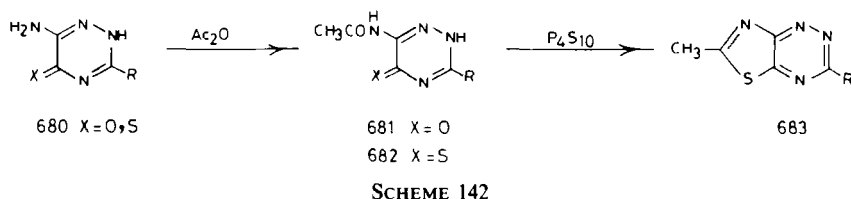
Only one isomeric system of the eight possible was reported during the period covered by this review.

[1,2,4]Triazino[4,3-b]benzisothiazoles

The reported example was the benzoanalogue of this ring system. Cyclization of (ethoxycarbonylmethyl)hydrazinobenzisothiazole **689** gave (90JIC861) triazinobenzisothiazole derivative **690**, which condensed with aromatic aldehydes to give arylidene derivatives **691**. These compounds are active against *S. aureus*, *Salmonella typhosa*, and *Shigella dysenteriae* (Scheme 145).



SCHEME 141



X. Triazolo[1,2,4]triazines

A. [1,2,3]TRIAZOLO[x,y-z][1,2,4]TRIAZINES

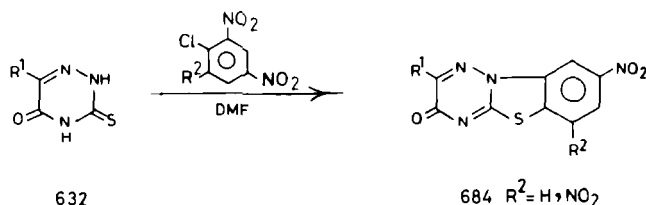
Two isomeric structures were reported.

1. [1,2,3]Triazolo[1,5-b][1,2,4]triazines

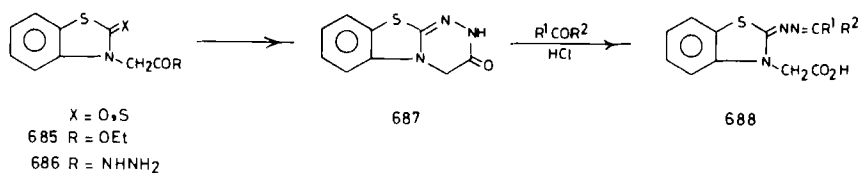
Diazotization of 5-amino[1,2,3]triazole **692** afforded (88BSB179) triazolo[1,5-*b*][1,2,4]triazine **694** as a result of a Dimroth rearrangement of the initially formed isomeric structure triazolo[5,1-*c*][1,2,4]triazine **693**. Molecular structure of **694** was determined by single X-ray diffraction (Scheme 146).

2. [1,2,3]Triazolo[1,5-d][1,2,4]triazines

Cyclization of the hydrazone derivatives of 4-benzoyl[1,2,3]triazole **695** by reaction with one carbon inserting agent such as an orthoester, an aldehyde, a ketone, or a phosgene afforded triazolotriazine **696** or **697** (88JHC743). The newly created C—N bond displays particular sensitivity due to the electron-attracting effect of the triazole ring (Scheme 147).



SCHEME 143



SCHEME 144

B. [1,2,4]TRIAZOLO[x,y-z][1,2,4]TRIAZINES

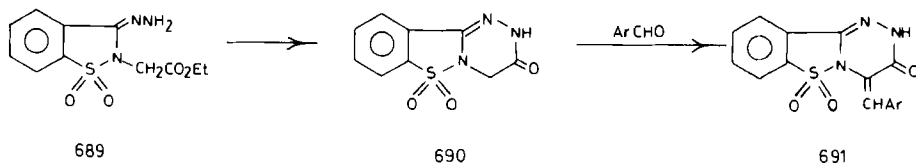
All nine [1,2,4]triazolo[x,y-z][1,2,4]triazines were reported during the period covered by this review. Some have been included in a review on [1,2,4]triazoles [90AHC(49)277].

1. [1,2,4]Triazolo[1,2-a][1,2,4]triazines

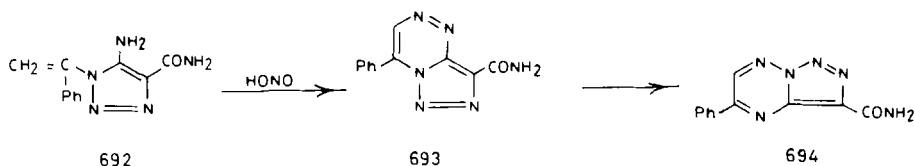
The first reported example representing this ring system was prepared (81LA1361; 87HCA1255) by silylation of *N*-acetyl acetamide with (tert-butyl)dimethyl silyl trifluoromethanesulfonate in the presence of triethylamine to give **698**, which underwent a Diels–Alder reaction with 4-phenyl[1,2,4]triazoline-3,5-dione **699** to give triazolotriazine **700**, which was converted by methanol to **701**. Similarly, **702** gave **703** [89JCR(S)66], whose X-ray structure was determined. Diels–Alder reaction of **699** with 1-substituted-2-pyridone **704** gave aza ethanotriazines **705** (76ZOR2270; 77GEP2704330; 78ZOR841) they are useful tranquilizers and cardiotonics (Scheme 148).

2. [1,2,4]Triazolo[1,5-b][1,2,4]triazines

A regioselective synthesis of 2-amino[1,2,4]triazinones **708** was reported (82JHC1583; 83JHC1671) by reaction of **706** with O-(2,4-dinitrophenyl)-hydroxylamine **707** as an amino transfer agent. Subsequent reaction of **708** with ammonia or amines, followed by ring closure with formic acid, provided **709**.



SCHEME 145

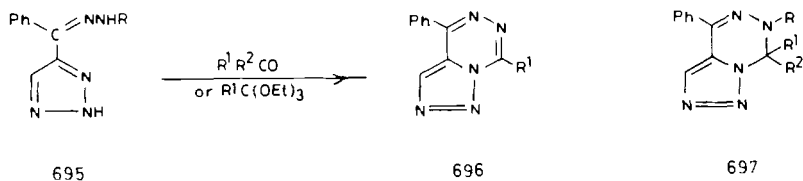


SCHEME 146

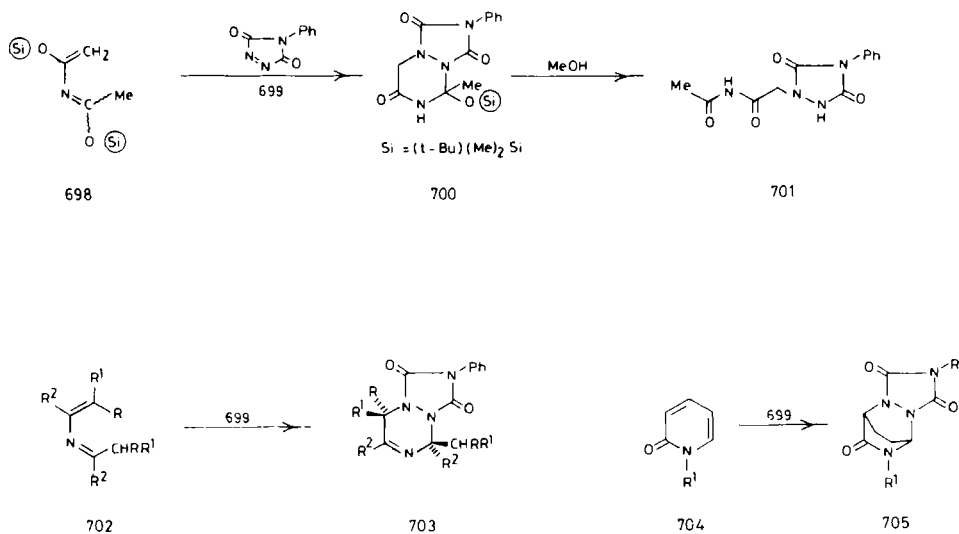
Triazolotriazines **711** were prepared (89EGP273834, 89EGP273835) by treating triazole **710** in methanol with potassium cyanide followed by acetic acid. These compounds act as intermediates for photographic emulsion stabilizers (Scheme 149).

3. [1,2,4]Triazolo[4,3-b][1,2,4]triazines

Acylation of 3-hydrazino-5,6-diphenyl[1,2,4]triazine **712** ($\text{R} = \text{R}^1 = \text{Ph}$) gave [79IJC(B)316] monoacyl derivative **713**, which on heating above its melting point or boiling in acetic acid gave [1,2,4]triazolo[4,3-b][1,2,4]triazines. This cyclization was also effected by the action of acyl chlorides or DMF-POCl_3 [79IJC(B)316]. The synthesis of the 7-substituted isomers **714** were reported by a similar approach. Thus, cyclizing the arylglyoxals with methylthioimidrazone gave the thio-methyl derivatives of the respective triazine, whose reaction with hydrazine gave 3-hydrazino-5-aryl[1,2,4]triazine **712** ($\text{R} = \text{H}$), which could be cyclized to **714** with a one-carbon cyclizing agent such as formic acid, ortho-formic acid, triethyl ortho-acetate, or cyanogen bromide (79JHC1393, 79USP4159375; 81USP298789). 6-Aryl[1,2,4]triazolo[4,3-b][1,2,4]triazines **715** were prepared (79JHC1393) from aryl glyoxaldoximes and semicarbazide and subsequent cyclization to 6-aryl[1,2,4]triazin-3(2H)ones. Its hydrazino derivative **712** was cyclized with one-carbon cyclizing agents to give **715**. The effect of substituents and the reagent on the orientation of annulation of the triazole ring in 6-substituted-3-hydrazino-5-hydroxy[1,2,4]triazine was studied [75BSF(2)857]. An electron-donor sub-



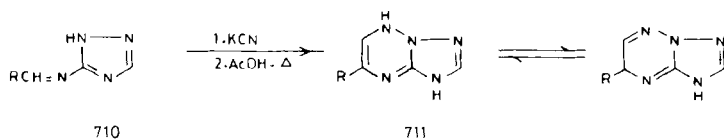
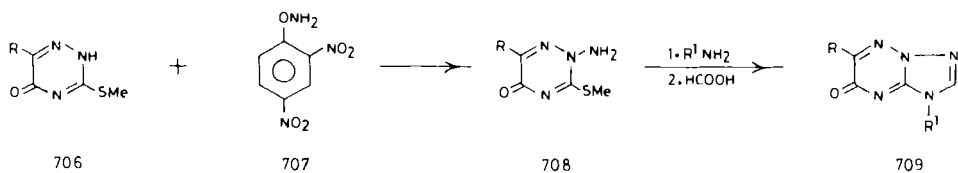
SCHEME 147



SCHEME 148

stituent at the 6-position leads to *s*-triazolo[4,3-*b*][1,2,4]triazines by the action of a carboxylic acid. This is a consequence of increasing the electron density on N-1 and N-2 [75BSF(2)857].

Condensation of hydrazino derivative **716** with formic acid gave triazolo[4,3-*b*]- and [3,4-*c*][1,2,4]triazines **718** and **719**. The reaction proceeded through N-2 acylation of the hydrazino group to give intermediate



SCHEME 149

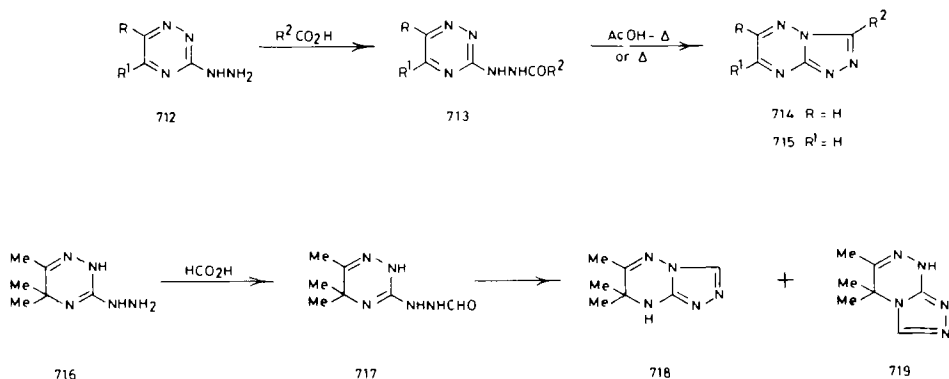
717, which was cyclized either at N-2 or N-4 of the triazine ring to give **718** and **719** (79JHC427) (Scheme 150).

Cyclization of 3-hydrazinotriazines **712** with cyanogen bromide afforded [76JCS(P1)1492] the hydrobromide of a weakly basic amine **721** via intermediate **720**. Deamination of **721** with pentyl nitrite gave triazolo [4,3-*b*][1,2,4]triazine **722**. Similarly, 7-oxo analogues were obtained (81JHC1353).

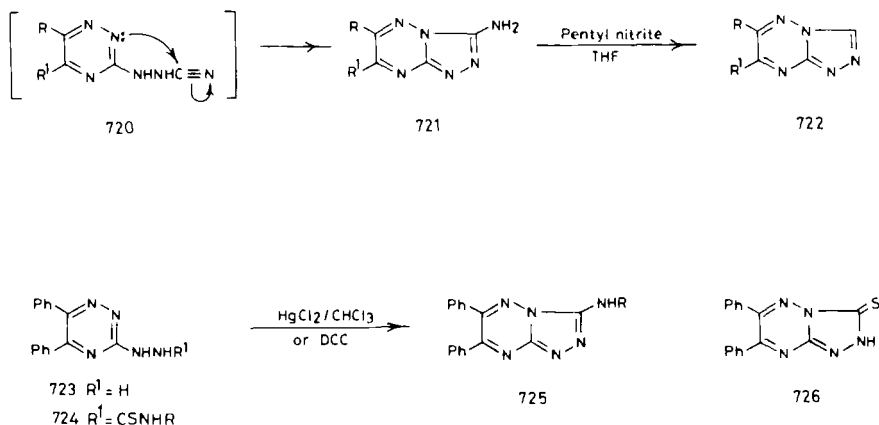
Condensation of hydrazine **723** with isothiocyanates gave thiocarbamoyl derivatives **724**. Their cyclodesulfurization to give aminotriazolotriazines **725** was carried out (88M591) by using mercuric chloride or dicyclohexyl carbodiimide. The conversion of **724** to **726** was accomplished by boiling in butyl alcohol (88M591). Compounds **724** and **725** were screened against P388 lymphocytic leukemia; **724** are toxic, whereas **725** are nontoxic (Scheme 151).

The synthesis of triazolotriazine derivative **728** starting from hydrazine **727** was carried out (89MI1) by a reaction with ethyl chloroformate, followed by thiation and methylation. The reaction of hydrazine with **728** led to selective replacement of the methylthio group at the 7-position by a hydrazino group to give **729**. The latter reacted with carbonyl compounds to afford the respective hydrazones. Cyclocondensation of **727** with formic acid and carbon disulfide gave (90MI4,8) triazolotriazine **730** and **731**, respectively.

Several derivatives of [1,2,4]triazolo[4,3-*b*][1,2,4]triazines have been obtained from 7-oxo[1,2,4]triazolo[4,3-*b*][1,2,4]triazine by successive thionylation of the carbonyl group to give **732** followed by methylation at the sulfur atom, replacement of the methylthio group of **733** with hydra-



SCHEME 150



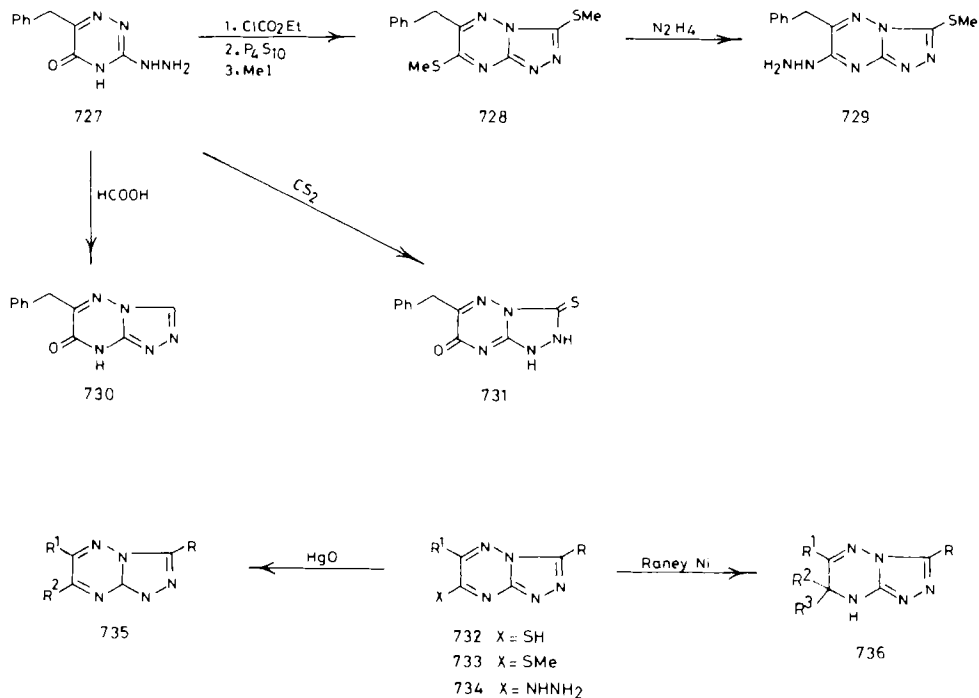
SCHEME 151

zine, and oxidation of 7-hydrazino derivative **734** with mercuric oxide (77JOC1018). A methyl group could be introduced into the 7-position on treatment of **735** with methyl magnesium iodide to give **736**. Desulfurization of triazine **732** with Raney-Nickel gave **736** ($R^2 = R^3 = H$), which on methylation gave **736** ($R^2 = H$, $R^3 = Me$) (79JHC427) (Scheme 152).

The alternative synthesis for this ring system was achieved by the condensation of an α -dicarbonyl compound with a suitably functionalized 3,4-diamino[1,2,4]triazole **737** to give **738** (73MI2; 77JOC1018). The 7-aryl isomers of **738** were obtained by the use of arylglyoxaldehydes as dicarbonyl compounds. The 6-isomer may also be obtained with it, depending on the structure of the dicarbonyl compound. This deviation from regioselectivity was attributed to the decreased reactivity of the 4-amino group due to the increasing steric bulk of the C-5 substituent. Another factor to be considered is the electronic effect of the aryl moiety on the carbonyl groups. On the other hand, the synthesis of the 6-aryl isomers could not be achieved from the reaction of aryl-glyoxaldehyde oxime, as prolonged heating gave the 7-aryl isomers as a consequence of its initial hydrolysis. They reduced edema orally in rats in the carrageenan assay test (81USP298789).

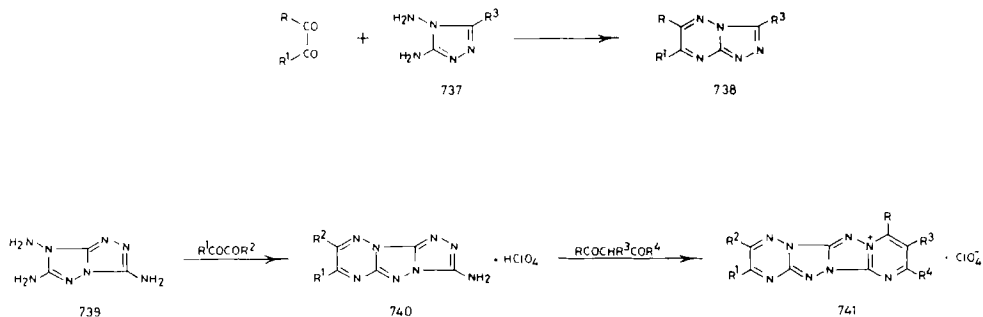
Tetracyclic ring system **741** was prepared by condensation of **739** with α -diketones to give **740**, whose treatment with β -diketones gave **741** (73MI1; 80UKZ1092) (Scheme 153).

The reaction of 3-hydrazinophenanthro[9,10-*e*][1,2,4]triazine **742** with carbon disulfide, thiourea, phenyl isothiocyanate, urea, and phenyl isocyanate led [77ZN(B)569] to the formation of phenanthro[9,10-*e*][1,2,4]-triazolo[4,3-*b*][1,2,4]triazines **743**. Alkylation of **743** in aqueous alkaline



SCHEME 152

solution led to the formation of the *S*-alkyl and not the *N*-alkyl derivatives. The structures of **743** were proved independently by a synthesis involving the condensation of phenanthraquinone with 3,4-diamino-5-mercapto[1,2,4]triazole [77ZN(B)569]. Cyclizing hydrazine **742** with for-



SCHEME 153

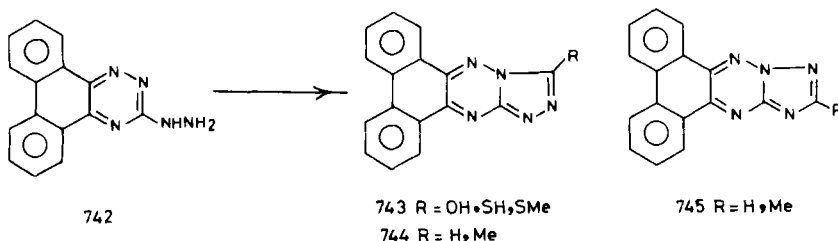
mic acid gave **744**, whose structure was proved by an independent synthesis [77ZN(B)569]. The formation of **745** (R = H) was also reported (80AP465). Although the reported mp is the same in both publications, there was no reference to the previous one [77ZN(B)569]. Similarly, the reaction with acetic acid gave **745** (R = Me). On the other hand, the authors (80AP465) gave structure **745** for the products without mention of a possible rearrangement. It is not clear whether the structure is **744** or that of a rearrangement product (Scheme 154).

Acenaphtheno[1,2-*e*][1,2,4]triazolo[4,3-*b*][1,2,4]triazine **747** was prepared (79AP147) by cyclizing 3-hydrazinoacenaphtheno[1,2-*e*][1,2,4]triazine **746** with formic acid. Reaction of **746** with sugars gave the hydrazones, which cyclized with iron(III) chloride to give **748** (93BCJ00). Similarly, the acetaldehyde derivative of **746** was cyclized to **748**. The structure of **748** (R = Me) rather than **747** (R = Me) was deduced by unequivocal synthesis of the latter by condensation of acenaphthenequinone with 3,4-diamino[1,2,4]triazole (Scheme 155).

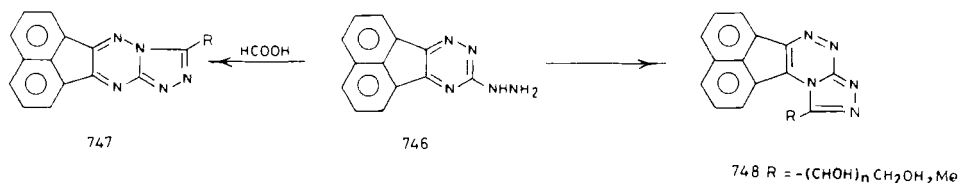
Hydrazinotriazine **749** was prepared by the condensation of the respective quinone with thiosemicarbazide followed by sequential cyclization, chlorination with phosphorus oxychloride, and reaction with hydrazine (88JHC1139). Cyclocondensation of **749** with formic acid or carbon disulfide gave triazolotriazines **750** (88JHC1139) (Scheme 156).

4. [1,2,4]Triazolo[5,1-*c*][1,2,4]triazines

This ring system may be assembled by constructing one of the two rings followed by the other. The order of the arrangement of methods in this part of the review will start by constructing the triazole ring onto a pre-formed triazine ring, followed by the reverse assembling of the rings. Otherwise, one of the most critical syntheses of this ring system is their formation as a result of a rearrangement of [1,2,4]triazolo[3,4-*c*][1,2,4]triazines.



SCHEME 154



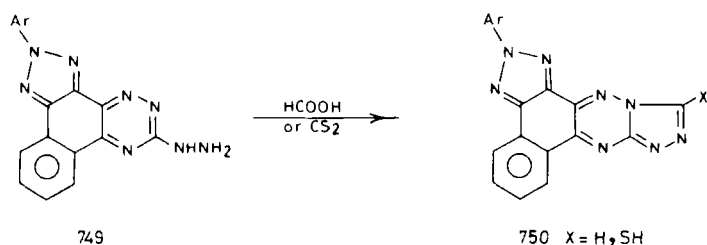
SCHEME 155

Diaminotriazines serve as precursors in this respect. Thus, **752** were prepared (87PHA547) by cyclocondensation of **751** with isothiocyanate. Methylation of **752** gave **753**. On the other hand, a similar condensation of **754** with phenylisothiocyanate, followed by cyclization gave triazolotriazine **755** (87PHA547). Rearrangement of oxadiazolium bromides **756** with hydrazine gave **757**, which thermally cyclized to **758** (78ZC136; 85PHA17) (Scheme 157).

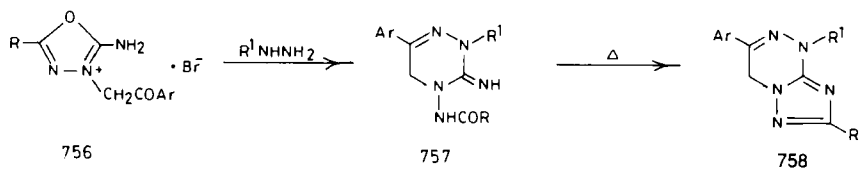
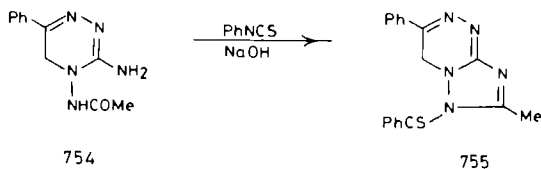
The reaction of *N*-amino heterocycles **759** and **760** with diaryl carbodiimide gave triazolotriazine **761** in good yield. In some cases the intermediate guanidines are isolated which by thermal or basic treatment cyclized (86H3363; 89H1607) to neutral or mesoionic compounds.

The ready synthesis of iminophosphoranes and their subsequent aza-Wittig reaction with isocyanates may depend on the substituent at position-3 [84S983; 86JCS(P1)2037; 89JCS(P1)247]. Thus conversion of **759** to **762**, followed by reaction with isocyanates gave [86JCS(P1)2037] **764**, whose ring cleavage gave triazolotriazinones **765**. On the other hand, reaction of **760** (R = NHR') with isocyanates led (84S983) directly to **765**, whose structures were determined by X-ray crystallography [86JCS(P1)2037]. The reaction of thiourea or its derivatives with iminophosphorane **763** led directly to **761** in moderate yield (89H1607) (Scheme 158).

The ready synthesis of iminophosphorane **767** from **766** and its subsequent conversion to benzylidene derivative **768** and aza-Wittig reaction



SCHEME 156



Cc1nc2n([N+](=O)[O-])c([N+](=O)[O-])n2c(=O)n1 (759, R = SMe)
Cc1nc2n([N+](=O)[O-])c([N+](=O)[O-])n2c(=O)n1 (760, R = NH₂)

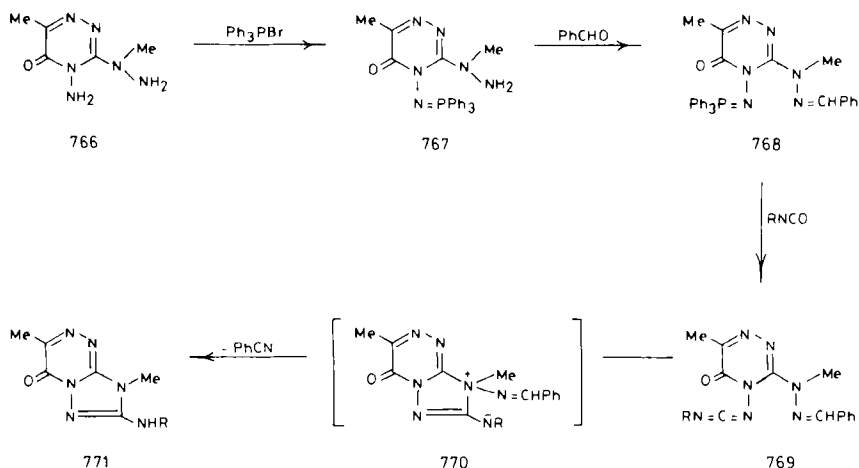
Reagents and conditions:
 1. $\text{ArN}=\text{C}=\text{NAr}$
 2. PH_3PBr_2
 3. ArNHCSNHAr
 4. R^1NCO (R = SMe)
 5. $\text{EtOH} - \text{H}_2\text{O}$

Products:
 761: Cc1nc2n([N+](=O)[O-])c([N+](=O)[O-])n2c(=O)n1 (R = SMe)
 762: Cc1nc2n([N+](=O)[O-])c([N+](=O)[O-])n2c(=O)n1 (R = SMe)
 763: Cc1nc2n([N+](=O)[O-])c([N+](=O)[O-])n2c(=O)n1 (R = NH₂)
 764: Cc1nc2n([N+](=O)[O-])c([N+](=O)[O-])n2c(=O)n1 (R = SMe)
 765: Cc1nc2n([N+](=O)[O-])c([N+](=O)[O-])n2c(=O)n1 (R = SMe)

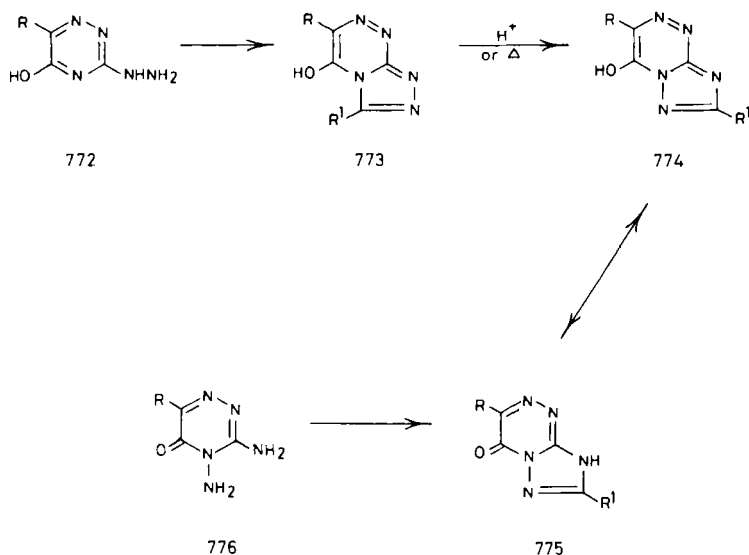
with aliphatic isocyanates gave **771**. Annulation occurs via carbodiimide **769** as an intermediate, which underwent nucleophilic attack by one nitrogen atom of the hydrazone moiety to give zwitterionic bicyclic intermediate **770**, which by internal proton abstraction undergoes elimination of phenyl cyanide to give **771** [89JCS(P1)247] (Scheme 159).

Cyclization of hydrazinotriazine **772** having an electron-attracting substituent at the 6-position with formic, acetic acid or an ortho ester gave triazolo[3,4-*c*][1,2,4]triazine **773**, which underwent rearrangement on heating or on treatment with acid to give triazolo[5,1-*c*][1,2,4]triazine **774**. The latter was also prepared by cyclization of diaminotriazinone derivative **776** [75BSF(2)857]. The presence of electron-attracting substituents in the 6-position of **772** increases the speed of transposition to the triazolo[5,1-*c*][1,2,4]triazine isomer [75BSF(2)864]. This is due to an inductive effect of the electron-attracting substituents and not due to a mesomeric effect as a consequence of the difficulty of the substituent to be coplanar with the triazine ring. The preferred tautomeric structures of the products are **775** containing a carbonyl group in which two neighboring nitrogen atoms are of different types [76BSF(2)1178]. The study was done by comparing the UV spectra with those of analogues whose structures are fixed by the presence of *N*-methyl groups (Scheme 160).

The action of hydrazine on 1-acetyl-5-chloro[1,2,4]triazole **777** or **778** gave (77JOC1018; 82KGS1113) **779** and **780**, respectively. Dehydrogenation of **779** gave **781**. Condensation of 3-hydrazino[1,2,4]triazole **782** with



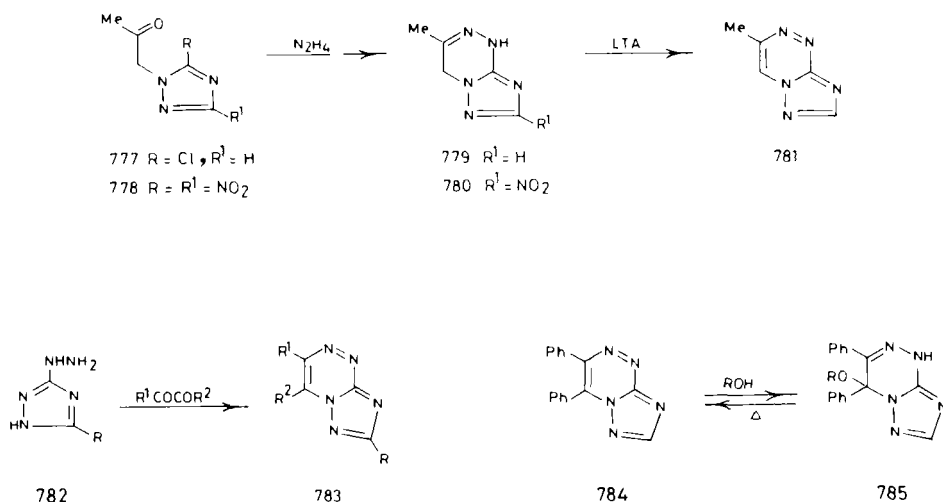
SCHEME 159



SCHEME 160

α -diketones gave **783**. Deamination of **783** ($R = \text{NH}_2$) with pentyl nitrite gave **784**, which is formed as a covalent hydrate, methanolate, or ethanolate. The alcoholates **785** could be isolated and reconverted to the aromatic system on heating or in hot acetic acid or pyridine [76JCS(P1)1492]. The crystal structure of **784** was studied [78AX(B)3409] (Scheme 161).

5-Amino-1*H*[1,2,4]triazoles were converted in neutral or weakly basic solution into the relatively stable diazonium betaines **786**, which reacted with active methylene compounds such as diethyl malonate, ethyl benzoylacetate, acetylacetone, benzoylacetone, dibenzoylmethane, benzoylacetonitrile, acetoacetanilide, ethyl cyanoacetate, and ethyl nitroacetate in the presence of sodium acetate to give **787**, which are cyclized to **788** [76JCS(P1)421; 78ZN(B)216; 90KFZ41]. In the case of ethyl acetoacetate and cyanoacetamide, the derived hydrazones were unstable and underwent spontaneous cyclization to the triazolotriazine. The respective hydrazone from ethyl cyanoacetate in aqueous ethanol gave a mixture of **789** ($R^2 = \text{CN}$) and **790**. In acetic acid the former was the main product, whereas in pyridine or collidine salts the latter was formed exclusively. 2-(1,2,4-Triazol-5-ylhydrazono)malononitrile **791** cyclized unambiguously to **793** [76JCS(P1)1496]. Mass spectrometry showed that the azole ring is more stable than the 1,2,4-triazine ring on electron impact. Similarly,



SCHEME 161

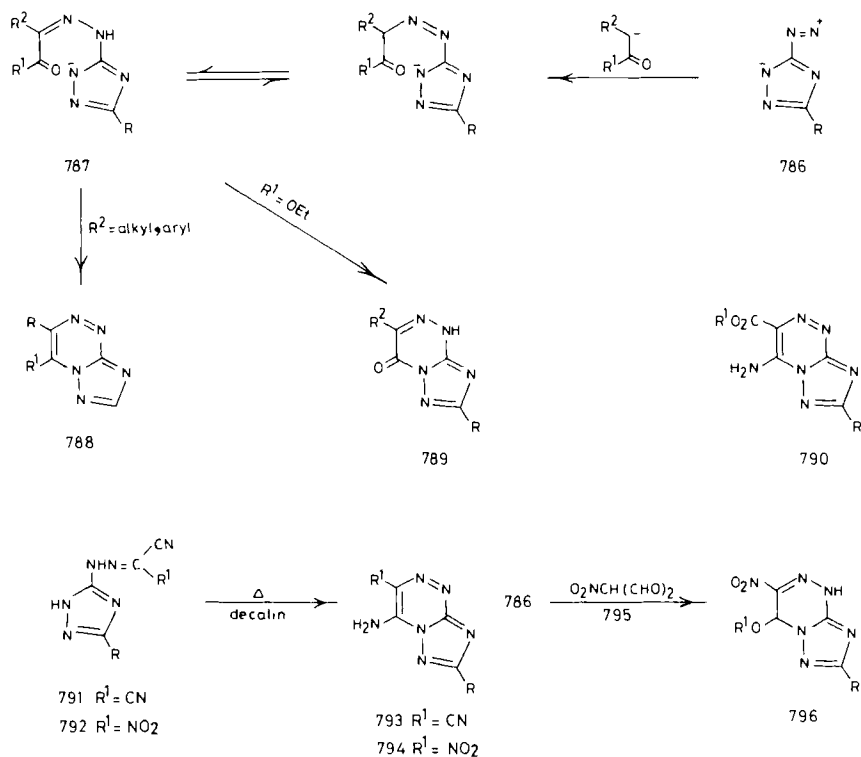
cyclization of **792** gave **794** (85KGS682). On the other hand, *s*-triazolo-[1,2,4]-*as*-triazines **796** were prepared from diazonium salts **786** by Japp-Klingemann reaction with **795** (86KGS662) (Scheme 162).

Cyclization of hydrazonyl chloride **797** with aniline gave triazolotriazine **798** ($R^2 = PhNH$) (80JHC209). Cyclization of **797** was also effected by the action of sodium acetate to give **798** ($R^2 = Cl$) (83JHC285). Cyclization of **799** by the action of sulfuric acid gave a triazolotriazine formulated as **800** or **801** (83JHC285).

Treatment of diazonium salts **786** with nitroethylacetate gave (80KGS1283) nitro derivatives **789** ($R^2 = NO_2$), which on heating in water led to an unexpected cleavage of the triazine ring to give **802** (91KGS700). Peculiarities were found on nucleophilic substitution of its nitro group. Its hydrazinolysis led to triazole derivative **803** (89KGS253). Treatment of **789** ($R^2 = NO_2$) with various halogenating agents gave **804** (80KGS1283; 82KGS1277), and with alkylthiols **805** (84URP1066999) (Scheme 163).

Reaction of the diazonium salt of 1,2,4-triazole with Melurdum's acid gave **806**, which cyclized to **807** (88JOC887). Methylation gave various derivatives, **808–811** (75GEP110662; 87KGS1543; 88JOC887). Its analogues with diethylamino alkyl derivatives were prepared as coronary vasodilator (75GEP110662). The pK_a values for **807** and its derivatives were determined (84KGS697) (Scheme 164).

Diazotized 3-amino[1,2,4]triazole reacted with 1,3-cyclohexanedione or its 5,5-dimethyl derivative and 1,3-indanedione to give (76M1199) tricyclic

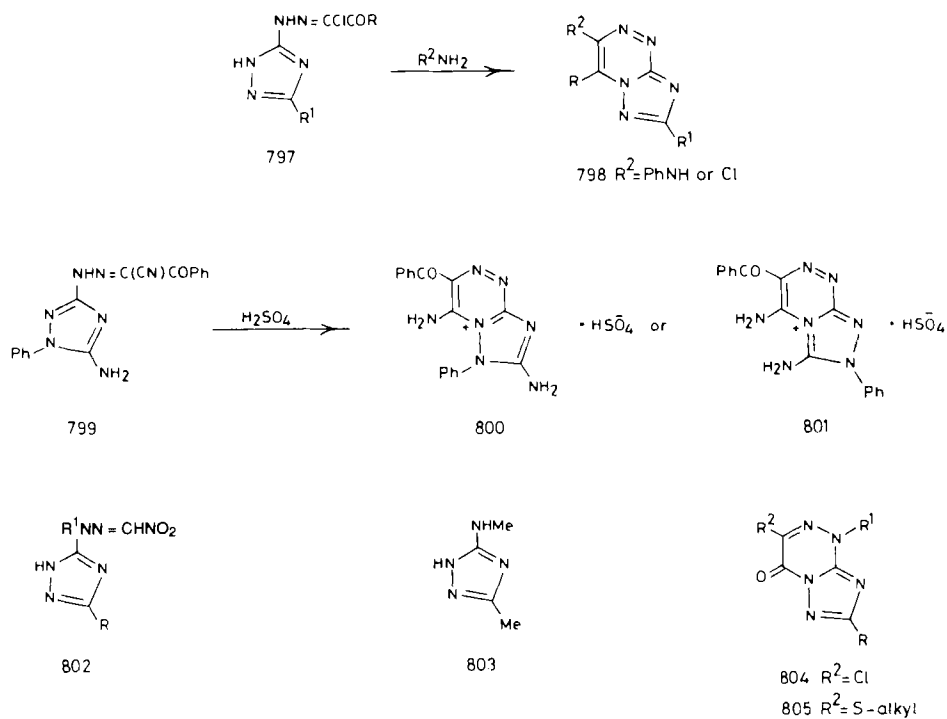


SCHEME 162

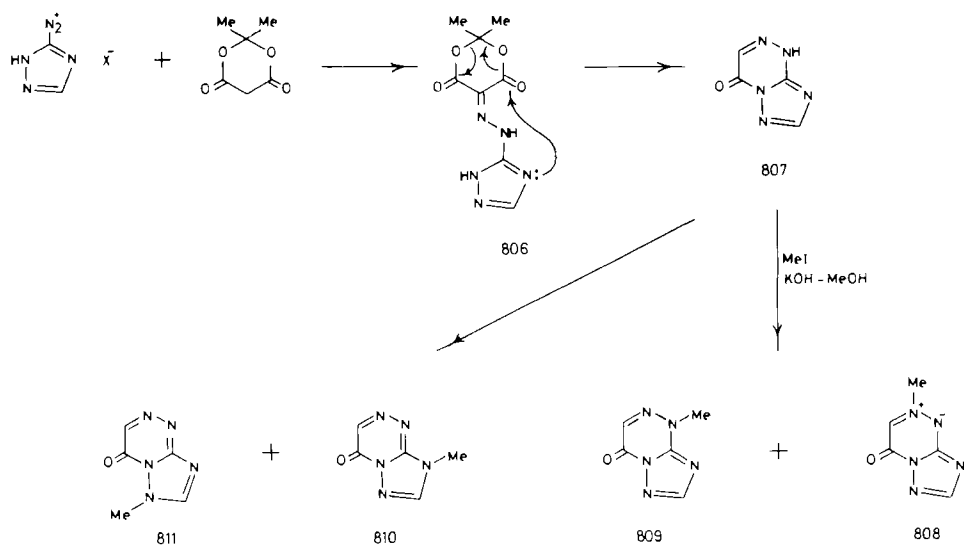
derivatives **813** or **814** and tetracyclic derivative **817**, respectively, via the corresponding hydrazones **812** and **816**. Compound **813** or its acetyl derivative is transformed in an acid-catalyzed reaction into the fully aromatic system **815** with simultaneous rearrangement.

Treatment of 3-diazo-3*H*-[1,2,4]triazole with 1-morpholinocyclohexene or 1-piperidiny cyclohexene gave triazotriazine **818** (87JOC5538), and with 1,1-dimethoxyethane afforded a mixture of two isomers of triazolo[3,4-*c*]triazine **819** and triazolo[5,1-*c*]triazine **820**, respectively [90JCS(P2)1943]. Compound **819** was the major product and it converted on storage to **820** (Scheme 165).

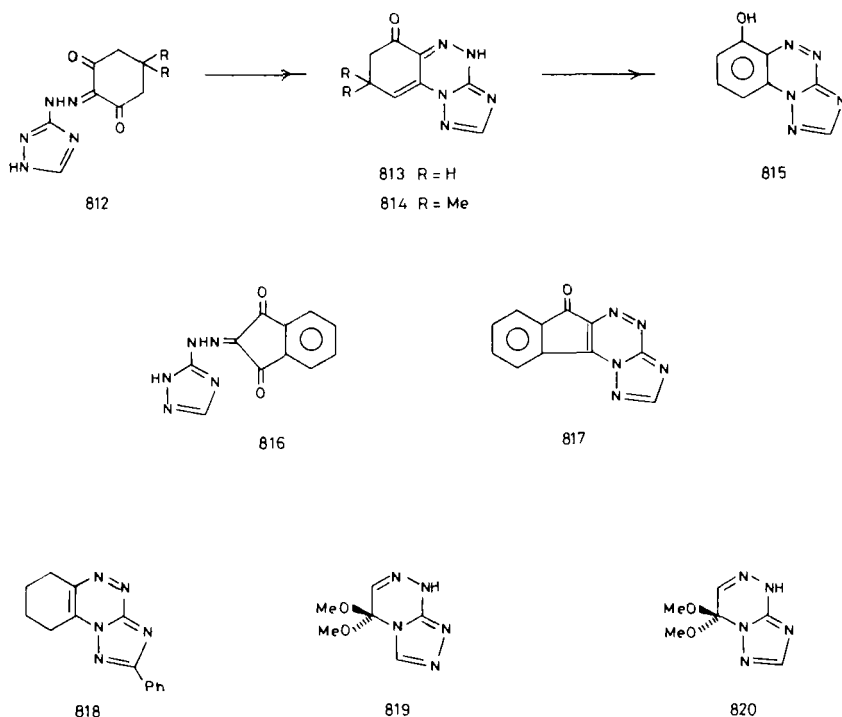
2-Substituted nitro derivatives of azolo[5,1-*c*][1,2,4]triazines were examined for their antimicrobial activity. They displayed antibacterial, antifungal, and antiviral activities. Structure-reactivity relationships have been reported (90KFZ39).



SCHEME 163



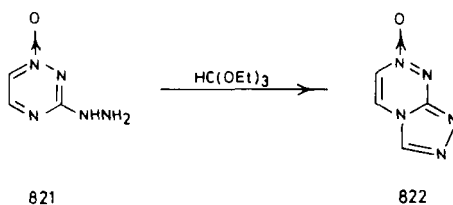
SCHEME 164



SCHEME 165

5. [1,2,4]Triazolo[3,4-*c*][1,2,4]triazines

Although, 3-hydrazino[1,2,4]triazines have been shown to be versatile precursors for the synthesis of [1,2,4]triazolo[4,3-*b*][1,2,4]triazines, 3-hydrazino-1,2,4-triazine-1-oxide **821** cyclized with triethyl orthoformate to give [1,2,4]triazolo[3,4-*c*][1,2,4]triazine **822**. Cyclization takes place at N-4 of **821** (80JOC5421) (Scheme 166).



SCHEME 166

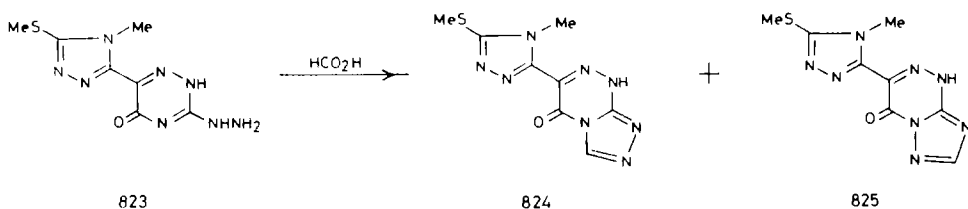
Reaction of hydrazine **823** with formic acid gave triazolo[3,4-*c*][1,2,4]triazine **824** and triazolo[5,1-*c*][1,2,4]triazine **825** [75BSF(2)864] (Scheme 167).

3-Hydrazinobenzo[1,2,4]triazines **826** were cyclized in a similar manner with orthoesters to give **828** [80ACH(105)189, 80MI5]. 1-Mercapto[1,2,4]-triazolo[3,4-*c*]benzo[1,2,4]triazines **833** have been prepared from thiosemicarbazide **831**, obtained from **826** by reaction with phenyl isothiocyanate, by thermal cyclization [80ACH(105)189, 80MI5]. Similarly, the oxygen analogue **832** was prepared from **826** via **830**. Various derivatives at the 3-position of triazole **834** were prepared. A series of pyrido[2,3-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazines have been prepared in a similar manner from **827** [80ACH(105)189], except that the oxo analogue of pyrido series **832** (X = N) is only prepared by direct ring closure from a starting material containing an activated reaction site in the semicarbazide moiety such as the *p*-fluorophenyl derivative. The oxo compound was also prepared [80ACH(105)189] from the thio analogue by the action of alkali peroxide. Narcosis-potentiating and analgesic ED₅₀ [80NEP8002120; 81JAP(K)81/08386] results have been reported (Scheme 168).

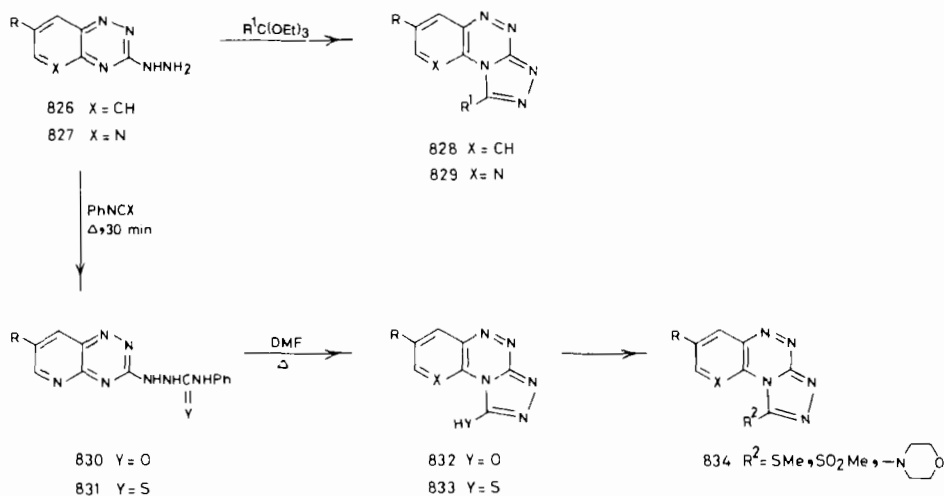
Hydrazine **835** underwent ring closure with one carbon cyclizing reagents to afford **837** and/or *N*-acyl derivatives **836**. The *N*-acyl derivatives underwent cyclization on treatment with phosphorus oxychloride. They were also prepared by the reaction of hydrazones **838** with thionyl chloride (84JHC1565). Compound **835** underwent ring closure with carbon disulfide and ethyl chloroformate to give **839** (Scheme 169).

Hydrazine **746** could be a precursor for this ring system through the formation of its respective hydrazones and oxidation with ferric chloride to give **748** (93BCJ00) and not the isomeric [1,2,4]triazolo[4,3-*b*][1,2,4]triazine ring.

A detailed study of the cyclization of the naphthalene derivative **840** with sulfuric acid to give (74JHC867) triazolotriazine **841** has been done (Scheme 170).



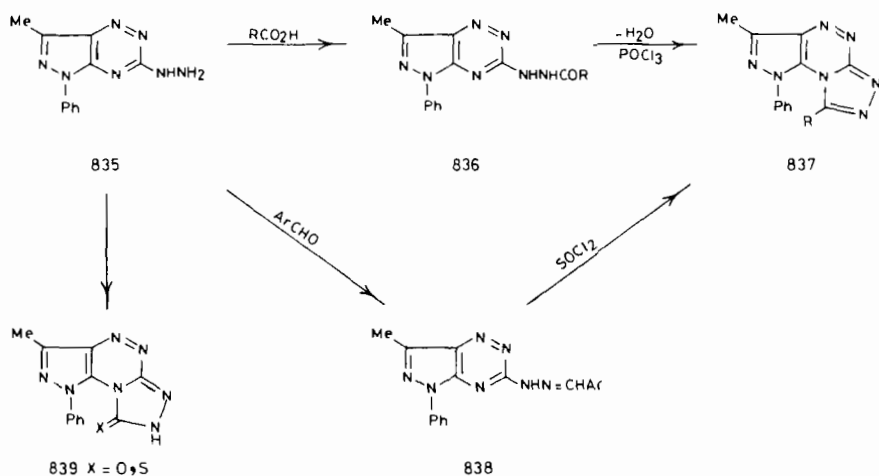
SCHEME 167



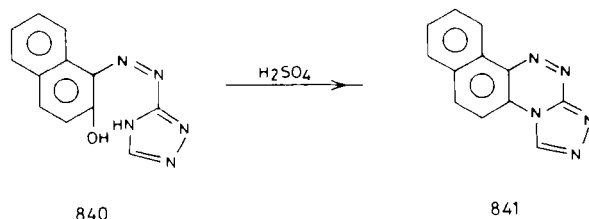
SCHEME 168

6. [1,2,4]Triazolo[1,5-d][1,2,4]triazines

6-Amino-5-hydrazino[1,2,4]triazin-3(2H)-one **842** represents an extremely interesting intermediate for the synthesis of that ring system and the following one via a regioselective ring closure with one carbon-inserting reagent. Thus, treatment of **842** with a variety of orthoesters and



SCHEME 169



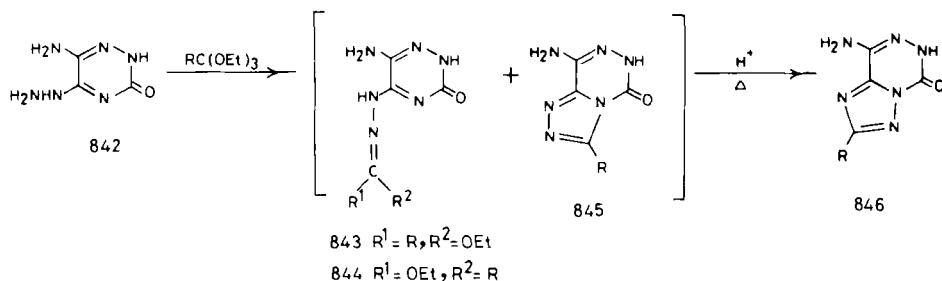
SCHEME 170

concentrated acid gave a mixture of open-chain derivatives such as **843** or **844** and [1,2,4]triazolo[4,3-*d*][1,2,4]triazin-3(2*H*)-ones **845**. The mixtures converted (82JHC1345) in warm aqueous acid to [1,2,4]triazolo[1,5-*d*][1,2,4]triazin-3(2*H*)-ones **846** by regiospecific ring closure at N-4 of the 1,2,4-triazine ring and subsequent Dimroth-like rearrangement. The use of more concentrated acid altered the course of the reaction and the ring closure at N-4 predominated; the 6-amino group was converted to the imidate ester. The product resulting from triethyl orthoacetate was conveniently prepared by the reaction of **842** with diethoxymethyl acetate to give **845** (R=Me), which rearranged by acid to **846** (R=Me) (Scheme 171).

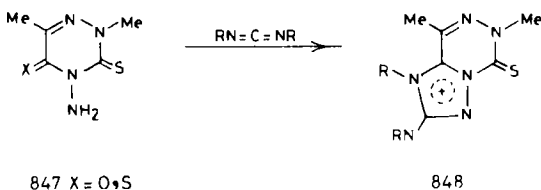
The reaction of *N*-aminotriazines **847** with diaryl carbodiimides led (88H161) directly to the new triazolotriazines **848**, which display mesoionic character (Scheme 172).

7. [1,2,4]Triazolo[4,3-*d*][1,2,4]triazines

The cyclization of 5-hydrazine-6-arylthio[1,2,4]triazin-3(2*H*)-ones **849** was effected by formic acid to give **950** (74MIP1). They are potentially useful as antibacterial, antiviral, and antimetabolic agents. Cyclization of



SCHEME 171



SCHEME 172

849 with cyanogen bromide gave **951** (81JHC1353). Reaction of **952** with ethyl dithioacetate gave **953** (88S778).

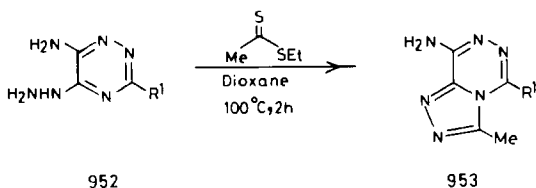
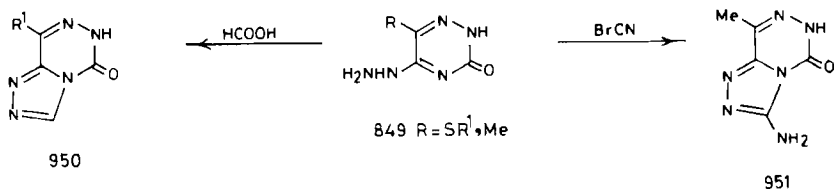
Although these cyclizations were reported to give triazol[4,3-*d*][1,2,4]triazine, care should be taken because a Dimroth-like rearrangement could easily take place (Scheme 173).

Cyclization of hydrazide **954**, with triethyl orthoformate gave a mixture of triazolo[4,3-*d*][1,2,4]triazines **955** and triazolo[1,5-*d*][1,2,4]triazines **956** in a ratio that was dependent on the substituent (81T4353) (Scheme 174).

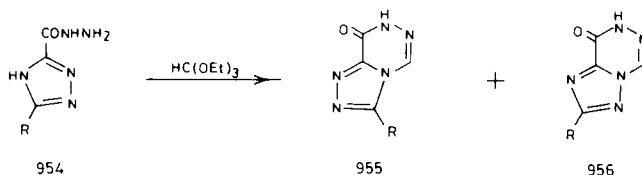
Tetrahydro[1,2,4]triazolo[4,3-*d*][1,2,4]triazines **960** were prepared by cycloaddition of **957** or oxazolotriazines **958** with benzonitrile N-4-nitrophenylimide **959** [91JCR(S)112] (Scheme 175).

8. [1,2,4]Triazolo[3,4-*f*][1,2,4]triazines

A facile ring closure at the N-1 nitrogen of the 1,2,4-triazine ring occurs to afford triazolo[3,4-*f*][1,2,4]triazinones **962** when **961** reacted with acids,



SCHEME 173



SCHEME 174

acid anhydrides, acid chlorides, orthoesters, cyanogen bromide, or carbon disulfide (79JHC555). Similarly, cyclization of hydrazine **963** with orthoesters gave **964** (84CCC65). Its benzo analogues were also prepared (Scheme 176).

Acylation of **965** gave **966**, whose cyclization with hydrazine or phenylhydrazine afforded [89IJC(B)829] triazolotriazines **967** or **968**, respectively (Scheme 177).

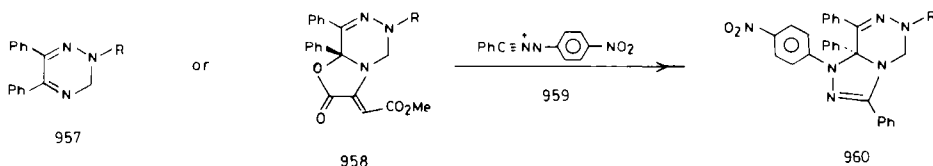
[1,2,4]Triazolo[3,4-*f*][1,2,4]triazines **971** were obtained by reduction of oxime **969** by iron powder in acetic acid, followed by sequential reaction with orthoesters to give (85JHC935) **970**, which was oxidized to **971** (Scheme 178).

3- β -D-Ribofuranosyl[1,2,4]triazolo[3,4-*f*][1,2,4]triazine **975** was prepared from the dehydrative coupling of **961** with 3,4,6-tri-*O*-benzoyl-2,5-anhydro-D-allonic acid **972** to give **973**, which on further ring closure gave **974**. Treatment of **974** with sodium methoxide in methanol gave **975**. Their antitumor activity was studied (86JMC2231) (Scheme 179).

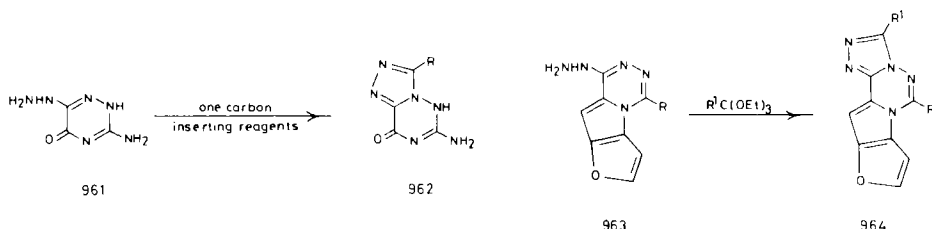
The C-nucleoside isostere of 9-(2-hydroxyethoxymethyl)-guanine **976**, was prepared as shown in Scheme 180. It showed no activity against herpes simplex virus types I and II in cell cultures (84JHC697) (Scheme 180).

XI. Oxadiazolo[1,2,4]triazines

Although there are various isomeric structures for this ring system, only one has been reported in the recent literature.



SCHEME 175



SCHEME 176

OXADIAZOLO[X,Y-Z][1,2,4]TRIAZINES AND [1,3,4]OXADIAZOLO[2,3-C][1,2,4]TRIAZINES

Title compounds **979** were prepared (75ZC219) by cyclizing **978**, prepared by hydrolysis of **977**, with phosphorus oxychloride. Reaction of **979** with isobutylamine gave triazolo[5,1-c]triazine **980** (Scheme 181).

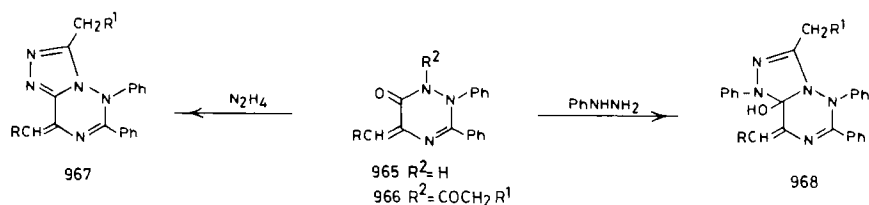
XII. Thiadiazolo[1,2,4]triazines

Isomeric structures similar to those for the oxadiazolo analogues can be drawn for this group of compounds, but more are reported here.

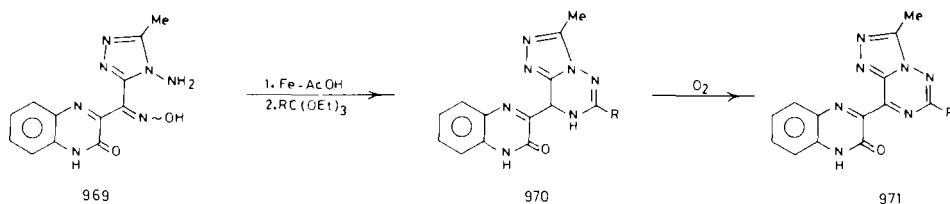
THIADIAZOLO[X,Y-Z][1,2,4]TRIAZINES

1. [1,3,4]Thiadiazolo[2,3-c][1,2,4]triazines

The synthesis has been described mainly by building the thiadiazole onto a triazine ring. However, one report has used thiadiazole **981** as starting material. Reaction of **981** with ethyl pyruvate gave **982** that was



SCHEME 177



SCHEME 178

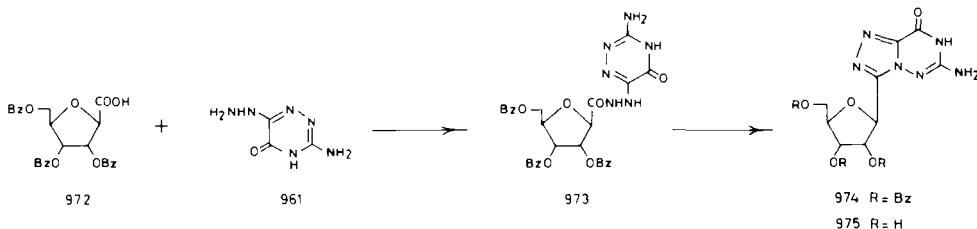
hydrolyzed to hydrazone **983**. Heating **983** in acetic acid gave **984** via a dehydrocyclization reaction (76JHC117) (Scheme 182).

The synthesis of **987** from **985** via **986** has been reported (83S759) by reaction of **985** with aryl isothiocyanates under neutral conditions. The reaction of 4-amino-6-anilino[1,2,4]triazine **988** with methyl iodide and then carbon disulfide gave **989** (90MI3, 90MI9).

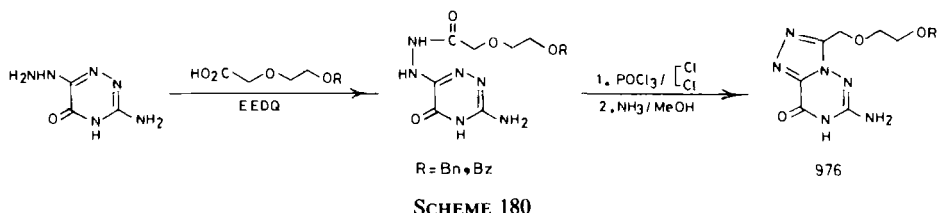
The sequential treatment of triazine derivative **990** with acyl chlorides and acetic anhydride and perchloric acid afforded (86H1031) thiadiazolo[1,2,4]triazinium perchlorates **991**. On the other hand, cyclocondensation of **992** with organic acids gave **993** [82JHC1577; 83JAP(K)58/180492] and **994** with aromatic aldehydes (84JIC552) (Scheme 183).

A Wittig-type reaction of iminophosphorane **995** with benzoyl and ethoxycarbonyl isocyanates gave (91T6747) thiadiazolotriazines **996**, whereas reaction of **995** with aromatic isocyanates afforded **997**. On the other hand, iminophosphorane **995** reacted with methyl and benzyl isothiocyanates to give **998**. Reaction of **995** with acid chlorides gave **999** (88H1935). All these compounds display mesoionic or zwitter ionic character (Scheme 184).

Cyclization of diaminotriazines **1000** with carbon disulfide gave **1001**, which were converted to triazininium salts **1003** and methylthio derivatives **1002** (82ZC219) (Scheme 185).



SCHEME 179



A ring-opening reaction of 1,3-diazetidines **1004** with thiobenzamide gave [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazine **1005** [89JCR(S)140] (Scheme 186).

2. [1,3,4]Thiadiazolo[3,2-*d*][1,2,4]triazines

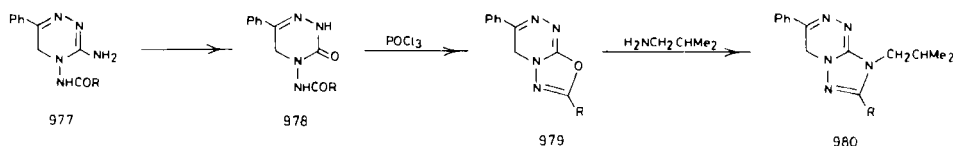
Reaction of iminophosphorane **1006** with ethoxycarbonyl isocyanate gave (91T6747) regioselectively thiadiazolotriazine derivatives **1007**, whereas treatment of **1006** with aromatic isocyanates in ethanol or in the presence of tetrafluoroboric acid afforded **1008** and **1009**, respectively. Similarly, **1006** with methyl isocyanate gave **1010** (91T6747) (Scheme 187).

3. [1,2,5]Thiadiazolo[3,2-*f*][1,2,4]triazines

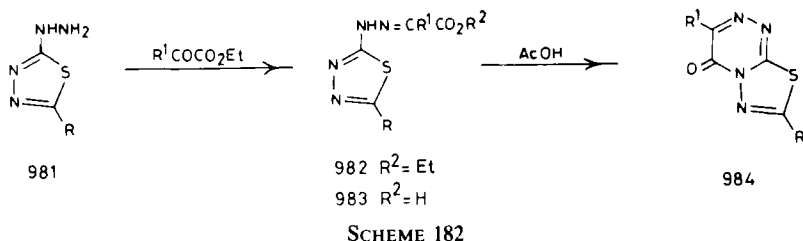
Heterocyclization of chlorosulfonyl isocyanate with ethyl-3-oxo-2-(aryldiazono)butanoates **1011** (2 : 1) gave thiadiazolotriazinediones **1012** (91H1517) (Scheme 188).

XIII. Tetrazolo[1,2,4]triazines

There are seven possible tetrazolotriazines. However, those bonded on edge **a** are not reported during the period covered by this review.



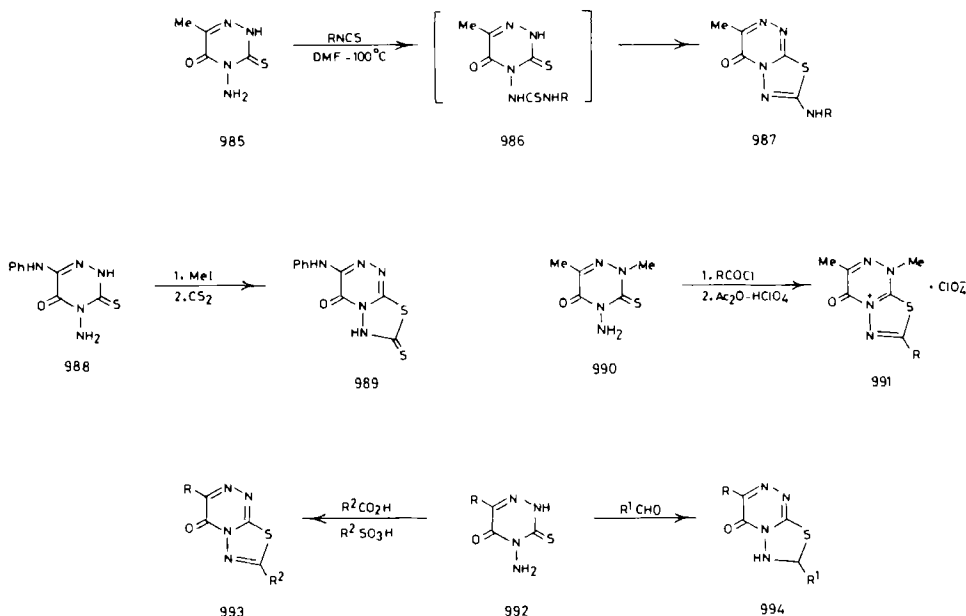
SCHEME 181



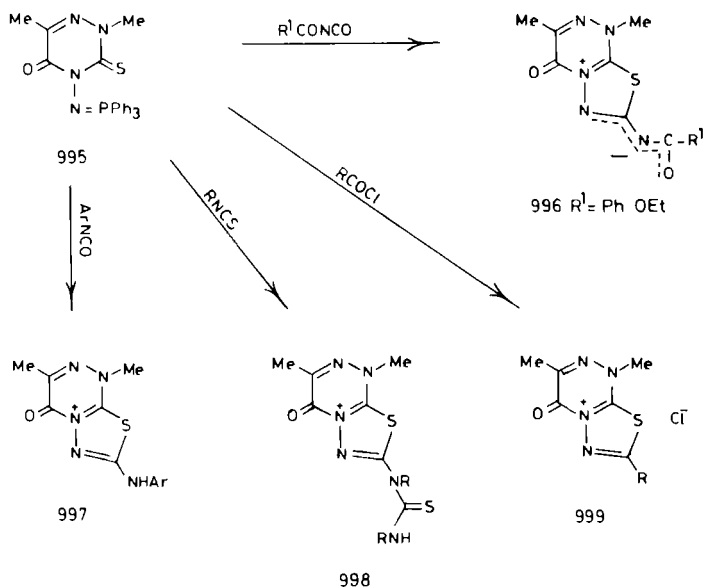
TETRAZOLO[X,Y-Z][1,2,4]TRIAZINES

1. Tetrazolo[1,5-b][1,2,4]triazines

Several 3-azido[1,2,4]triazines **1013** were prepared (76JOC2860; 77JHC1221) by treating the corresponding 3-hydrazino derivatives with nitrous acid. Azidotriazines **1013** were spontaneously cyclized to tetrazolo[1,5-*b*][1,2,4]triazines **1014** rather than their isomers **1015**. These transformations were studied using nuclear magnetic resonance and infra-



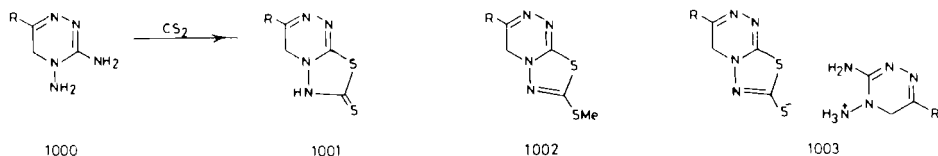
SCHEME 183



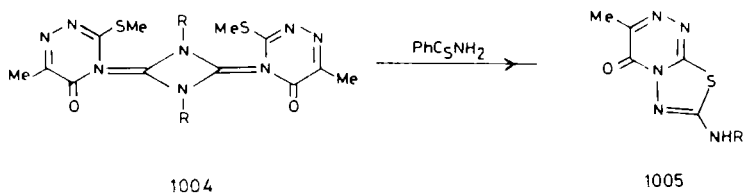
SCHEME 184

red spectroscopic methods. The structures of tetrazolo triazines **1014** were proved by X-ray crystallography (76JOC2860). 3-Hydrazinoacenaphtho[1,2-*e*][1,2,4]triazine was transformed in a similar manner (79AP147) into acenaphtho[1,2-*e*][1,2,4]triazino[2,3-*d*]tetrazole.

Naphtho analogues, naphtho[2,1-*e*]tetrazolo[1,5-*b*][1,2,4]triazine, naphtho[1,2-*e*]tetrazolo[1,5-*b*][1,2,4]triazine, and naphtho[2,3-*e*]tetrazolo[1,5-*b*][1,2,4]triazine, were prepared (82JOC3168; 84JOC3199) by cyclization of the respective hydrazine with sodium nitrite in acetic acid or by azide displacement of a leaving group. Elucidation of the site of annulation of the tetrazole ring was accomplished by X-ray analysis and ^{13}C -NMR spectroscopy (Scheme 189).

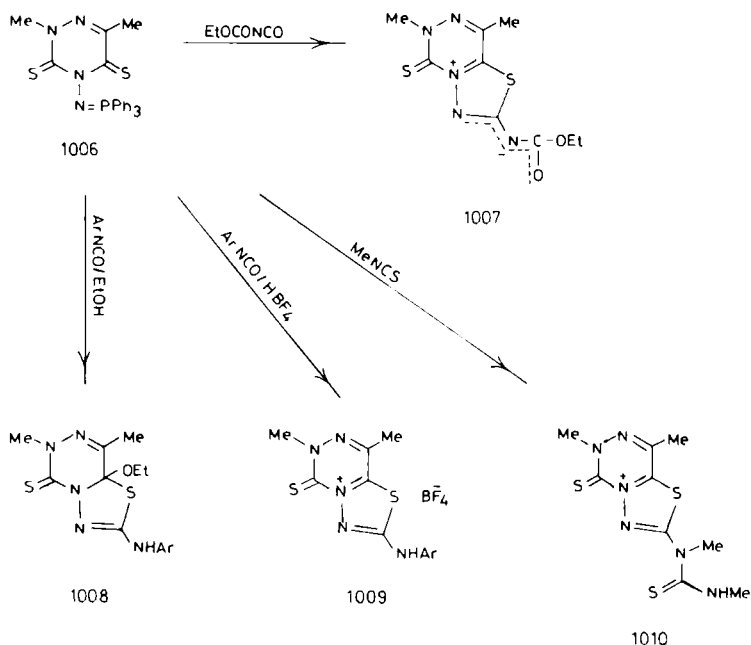


SCHEME 185

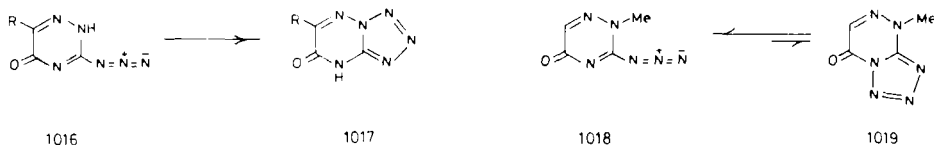


SCHEME 186

The presence of a 5-oxo group in the 1,2,4-triazines, as in 3-hydrazino-2,5-dihydro-5-oxo[1,2,4]triazines, does not alter the direction of cyclization by the action of nitrous acid. The initial products are azido compounds **1016**, which can cyclize spontaneously to tetrazolo[1,5-*b*][1,2,4]triazines **1017** (77JHC1221, 77JOC1866) rather than the previously reported isomeric structure. On the other hand, when the cyclization onto N-2 is impossible, as in derivative **1018**, the azidotetrazolo equilibrium **1018** \rightleftharpoons **1019** exists (76JOC2860; 77JOC1866). It exists in the solid state at least as the tetrazole derivative (Scheme 190).



SCHEME 187



SCHEME 190

amounts (79JOC1823). The tautomeric equilibrium of **1031** and its linear and angular tetrazoles was examined (82JOC3886). Electron-donating substituents and polar solvents stabilized the tetrazole over the azide and the ratio of the linear and the angular isomers was dependent on the substituents (Scheme 193).

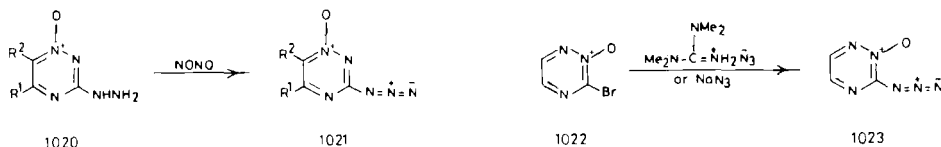
Coupling of the diazotetrazole with ethyl cyanoacetate gave **1034**. Its cyclization in boiling acetic acid or pyridine afforded **1035** as the major product in addition to **1036**. Mass spectral fragmentation of **1035** confirmed that the azole ring is more stable than the 1,2,4-triazine ring on electron impact [76JCS(P1)1496] (Scheme 194).

3. Tetrazolo[1,5-d][1,2,4]triazines

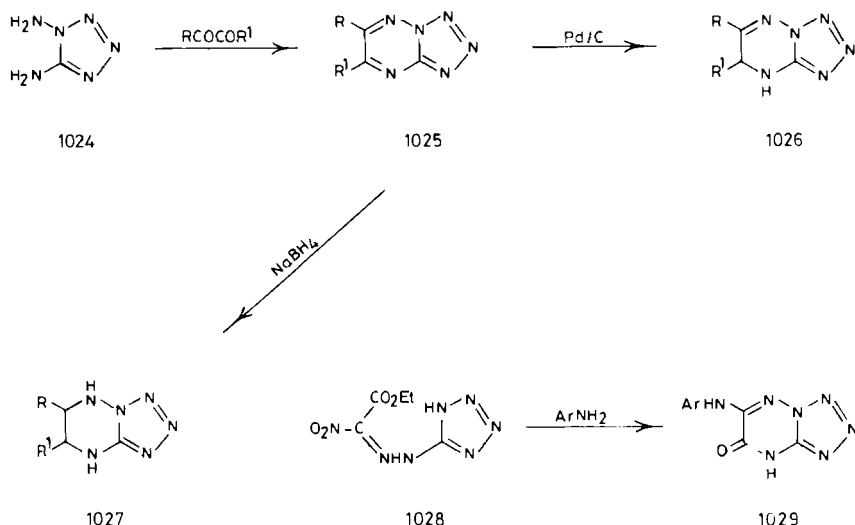
Thermolysis of the pyrazoline **1037** in chlorobenzene gave (76TL2513) triazinotetrazole **1038**, which on further heating decomposed to **1040** and **1039**. The reaction occurred by sequential ring expansion and contraction (Scheme 195).

4. Tetrazolo[5,1-f][1,2,4]triazines

Compound **961** has been converted into 3-amino-6-azido-5(2*H*)[1,2,4]triazinone **1041**, which was employed in a study of azide-tetrazole equilibrium affording 6-amino-8(5*H*)tetrazolo[5,1-*f*][1,2,4]triazinone **1042** (79JHC555) (Scheme 196).



SCHEME 191



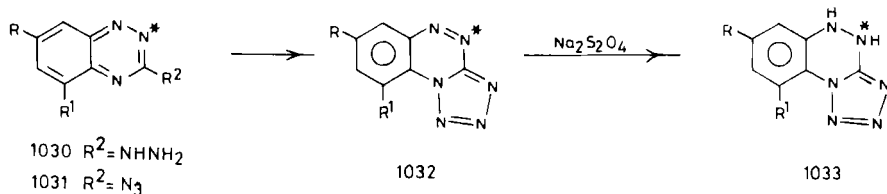
SCHEME 192

Appendix

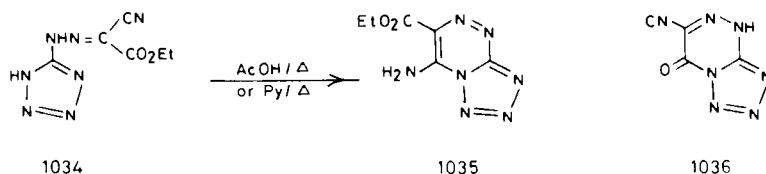
The literature that became available to us after this review was written is discussed here.

Aroylation of 3-arylhydrazonoisatin with aroyl chlorides gave **1043**, which cyclized with ammonium acetate to give [1,2,4]triazino[5,6-*b*]indole **1044** (92MI1). Derivatives of **1045** were prepared (92MI1). Cyclocondensation of 5-ethyl-3-hydrazino-5*H*[1,2,4]triazino[5,6-*b*]indole **165** with succinic anhydride in acetic acid gave pyridazinedione derivative **1046** (90MI7) (Scheme 197).

Furo[3,4-*e*][1,2,4]triazines **204** (91MI1) were prepared by the reaction of **199** or its analogues with aroylhydrazines in the presence of ammonium acetate in acetic acid. Similarly, the respective 3,3'-bis(furo[3,4-*e*][1,2,4]triazine) was prepared by reacting **199** with oxalic acid hydrazide (91MI5).



SCHEME 193



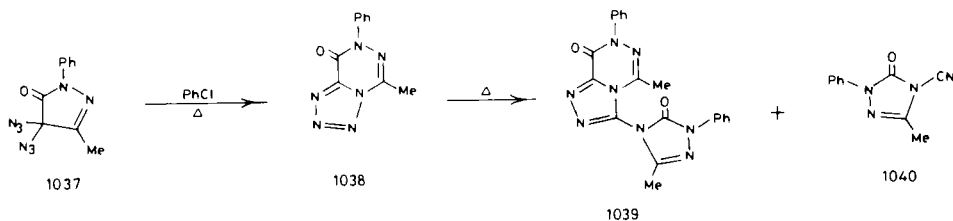
SCHEME 194

Pyrimido[5',4':4,5]pyrazolo[3,2-c][1,2,4]triazine derivatives **1049** and **1050** were prepared by treatment of diazo compound **1048**, prepared from **1047**, with pentane-2,4-dione and ethyl acetoacetate, respectively [92JCS(P1)239].

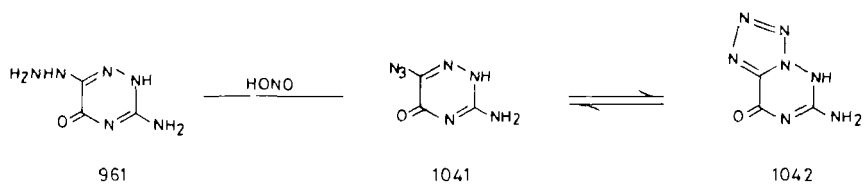
Cyclocondensation of **632** with dibromoethane in the presence of sodium ethoxide gave 2,3-dihydro-6-benzyl-7*H*-thiazolo[3,2-*b*][1,2,4]triazin-7-one, whose structure was confirmed by X-ray analysis (91MI7).

Naphtho[1',2':4,5]thiazolo[3,2-*b*][1,2,4]triazines **1052** were prepared by cyclocondensation of aminoiminonaphthothiazole **1051** with an acetylenedicarboxylate. Methyl ester **1052** was tested *in vitro* for anti-HIV activity and was inactive (91MI6).

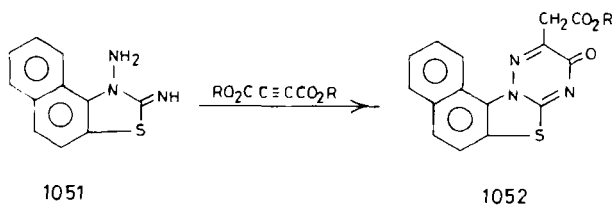
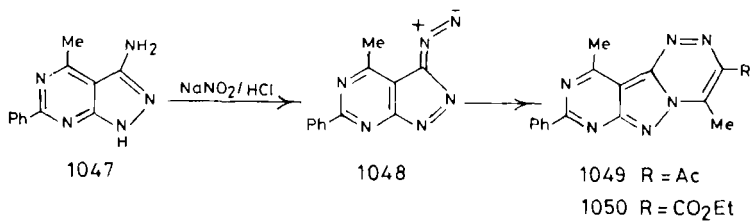
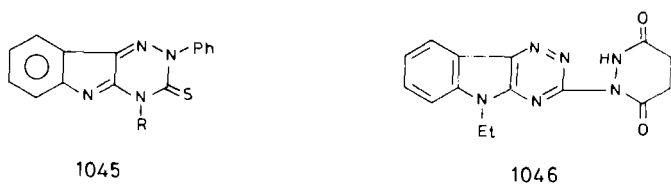
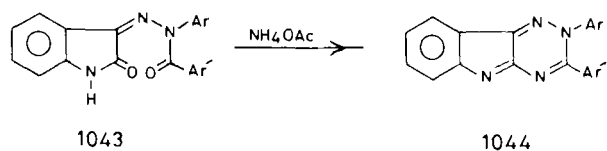
A derivative of **163**, 3-(2-morpholinoethylthio)[1,2,4]triazino[5,6-*b*]indole dihydrochloride, is used as a thrombolytic (91URP1672373). Derivatives of the pyrazolo[5,1-*c*][1,2,4]triazines were used as a constituent of silver halide color photographic supported material, which showed good color reproducibility [91JAP(K)03/291649]. The protective action of [1,2,4]triazino[4,3-*a*]benzimidazoles as corrosion inhibitors was studied (91MI8).



SCHEME 195



SCHEME 196



SCHEME 197

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Developments in the Chemistry of Thiopyrans, Selenopyrans, and Teluopyrans

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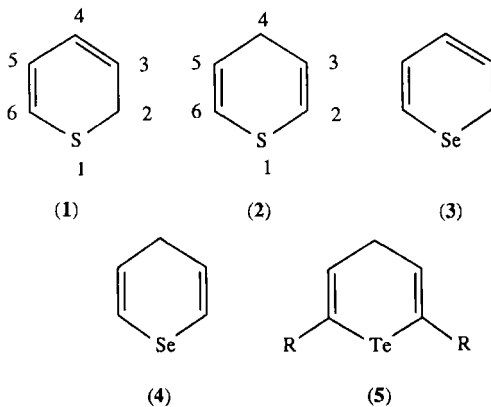
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I. Introduction

The chemistry of pyrans and their heteroanalogs has developed significantly since 1983, when it was first reviewed by one of the authors (83AHC145). To avoid undue length to this article, only the titled heteropyrans are treated and the discussion of the I-oxygen analogs will be published in the future.

In addition to various derivatives of the known parent heterocycles 1–4, the first teluopyrans 5(R = *t*-Bu, Ph) have been reported (88M11).

Except for several chapters in the comprehensive monograph on heterocyclic chemistry (84M11) no special articles covering the recent past are available. This review is an attempt to discuss the literature up to Volume 117 (1992) covered by *Chemical Abstracts* together with some accessible papers published in 1993. Only isolable or spectroscopically identifiable thio-, seleno-, and teluopyrans without exocyclic double bonds (heteropyrones and heteropyranylidene derivatives) are considered. All benzo derivatives and their annulated heteroanalogs (spiroheteropyrans) are excluded.



II. Nomenclature

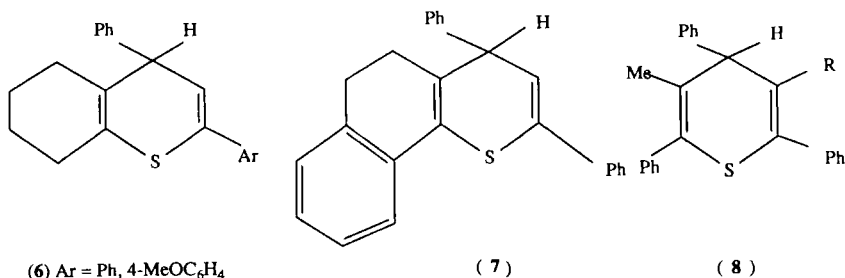
Depending on the position of the sp^3 carbon atom, the heteropyrans are usually classified as *2H*- and *4H*-isomers, although more systematic nomenclature (2- and 4-thiines, 2- and 4-selenines, 2- and 4-telurines or even -tellurines) may be recommended (84MI1). The numbering of the heterocyclic rings is shown in **1** and **2**.

III. Synthesis from Acyclic Precursors

The expressions "acyclic" or "cyclic" precursors indicate whether a heteropyran ring does or does not occur during a given synthesis. No importance is attributed to the fact that reactants may already contain a ring.

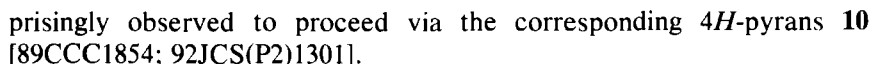
A. THIOPYRANS FROM 1,5-DICARBONYL COMPOUNDS

The standard procedure consisting in the heterocyclization of 1,5-diketones with hydrogen sulfide in the presence of protic acids (83AHC145, Section III,B) has been applied to the synthesis of *4H*-thiopyrans **6**, **7** and some others (80KGS1337; 82MI1; 84KGS898) and improved using ZnS instead of H_2S (90URP1583421). The acidic medium can cause additional disproportions and/or air-oxidation of the products, for example, **8**, to corresponding thiopyrylium salts and tetrahydrothiopyrans (80KGS1337, 80ZOR178; 82MI4).



4,4-Diphenyl-4*H*-thiopyran (**9**) was prepared by application of the known two-step procedure involving the 2,6-dichloro intermediate from the corresponding bis-dimethylacetal (82CJC574).

The second approach using P_4S_{10} in boiling xylene as cyclization agent was applied to the synthesis of 2,4,4,6-tetraaryl derivatives **11** and sur-

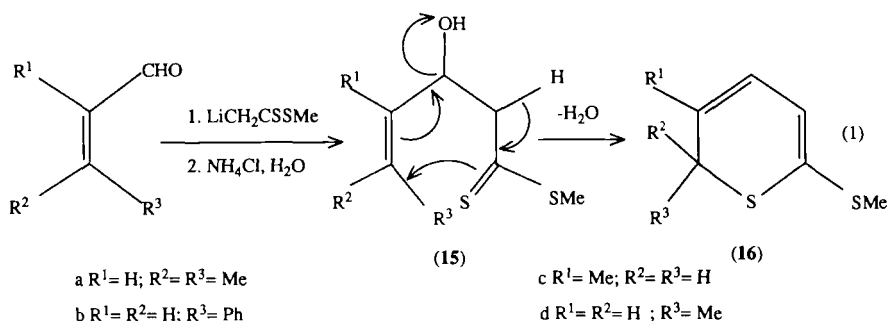


- | | | |
|---|-----------------------------------|---|
| a $R^1 = R^2 = R^3 = H$ | a $R = H$ | a $R = 4\text{-MeOC}_6\text{H}_4$, $R' = H$ |
| b $R^1 = R^2 = H$, $R^3 = Ph$ | b $R = Ph$ | b $R = 4\text{-MeOC}_6\text{H}_4$, $R' = Ph$ |
| c $R^1 = R^2 = H$, $R^3 = 4\text{-MeOC}_6\text{H}_4$ | c $R = 4\text{-BrC}_6\text{H}_4$ | c $R = R' = 4\text{-MeOC}_6\text{H}_4$ |
| d $R^1 = Me$, $R^2 = R^3 = H$ | d $R = 2\text{-FC}_6\text{H}_4$ | d $R = Ph$, $R' = H$ |
| e $R^1 = H$, $R^2 = R^3 = Ph$ | e $R = 4\text{-MeOC}_6\text{H}_4$ | e $R = R' = Ph$ |

2 and 6 led to bis-selenols **14a–14c** (82KGS704, 82MI3, 82ZOR2595). The use of trifluoroacetic acid in the cyclization procedure accelerated the formation of bis-selenols **14d** and **14e** from **12a** and **12b** as well as disproportion products from **12a**, **12b**, and **13a** (81KGS640; 84KGS1634). Mechanisms both involving and not involving intermediate carbocations have been discussed (81KGS640; 82ZOR2595; 84KGS1364).

C. THIOPYRANS FROM THIOENOLATES

A new route to 2*H*-thiopyrans has been found in the cyclocondensation of thioenolates with α,β -unsaturated carbonyl compounds. The starting sulfur component can be methyl thiol-thione-ethanoate (90BSF446) or a β -thienol-aldehyde (90ZC247) as shown by Eqs. (1) and (2), respectively.

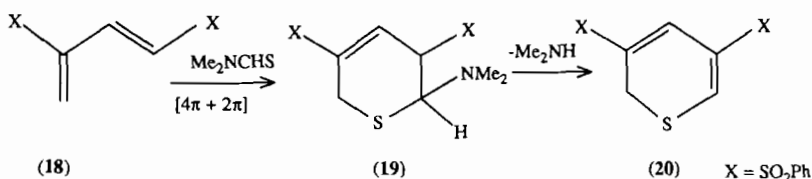
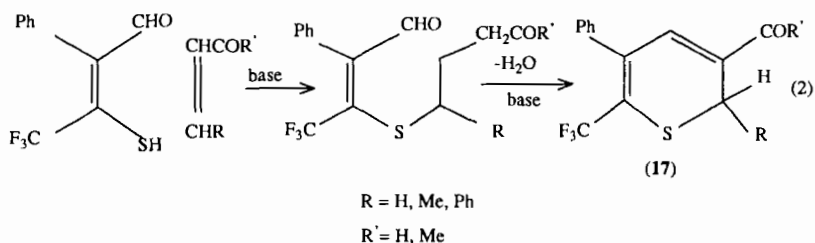


The final transformation of **15** to **16** was found to exhibit a significant dependence on substituents. 2*H*-Thiopyran **16a** arose spontaneously in 32% yield, while 53% of **16b** was obtained together with 41% of its precursor **15b**. No formation of thiopyrans **16c** and **16d** was observed in the case of less substituted hydroxy derivatives **15c** and **15d** (90BSF446). The preparation of 3-acyl-2*H*-thiopyrans **17** was reported to be stimulated by dicyclohexylamine (90ZC247). More extensive substituent patterns as well as the use of aqueous NaOH in similar reactions were described (86GEP234674; 875456).

D. THIOPYRANS FROM THIOAMIDES

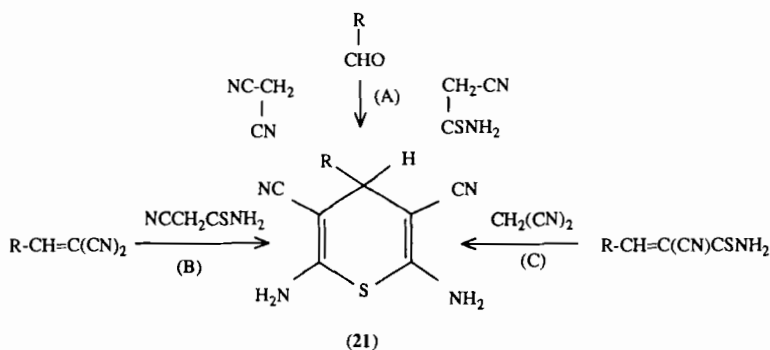
2-Thiopyrans can be synthesized by a $[4\pi + 2\pi]$ cycloaddition involving one dimethylthioformamide component. The latter was observed to react with the diene **18** generated *in situ* ($\text{PhSO}_2\text{CH}_2\text{CH}=\text{C}(\text{SO}_2\text{Ph})\text{CH}_2\text{SO}_2\text{Ph} + \text{Et}_3\text{N} \rightarrow \textbf{18} + \text{Et}_3\text{NHSO}_2\text{Ph}$) giving the 3,5-disubstituted 2*H*-thiopyran **20** via dihydrointermediate **19** (89JOC4232; 91JOC2713).

The same procedure was employed for the preparation of 2-substituted 4,6-bis-benzenesulfonyl-2*H*-thiopyrans (92JOC3540).



The known but newer, more elaborate approach to 4*H*-thiopyrans by procedures A, B, and C (Scheme 1) resembles the Hantzsch-like syntheses of 4*H*-pyrans (83AHC145, Section III,D). The results are summarized in Table I for 3,5-dicyano products **21**. The chemistry of cyanothioacetamide as the key starting component has also been reviewed (86H2023; 87H205). Cyclocondensations A to C usually proceed under mild conditions and afford **21** in satisfactory yields.

Some modifications of the procedures B and C have been reported for the preparation of 5-(benzothiazol-2-yl)- or 5-acetyl derivatives **22** (88AP509) and **23** [87ZN(B)107]. The use of the sulfur precursor **24** (85S432) or nonsulfur starting components **26** [87ZN(B)107] led to biheterocyclic 4*H*-thiopyrans **25** or **27**, respectively.



SCHEME 1

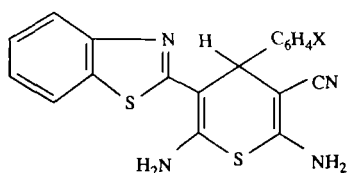
TABLE I
4-SUBSTITUTED 2,6-DIAMINO-3,5-DICYANO-4H-THIOPYRANS (21) PREPARED
ACCORDING TO SCHEME I

R	Procedure	Reference
H	A	91JCR(S)116; 92G299
Ph	A,B,C	85H3107; 86LA1639, 86ZN(B)781; 89BCJ3768, 89ZOR622, 89ZOR1323
2-XC ₆ H ₄ ^a	A,B,C	89BCJ3768
3-BrC ₆ H ₄	A,B,C	89BCJ3768
4-XC ₆ H ₄ ^b	A,B,C	85H3107; 86LA1639, 86ZN(B)781; 89BCJ3768, 89ZOR1323
X, Y-C ₆ H ₃ ^c	A,B,C	89BCJ3768
2-Furyl	B,C	89BCJ3768, 89ZOR622
2-Thienyl	B,C	89BCJ3768; 91IZV1643
3-, 4-Pyridyl	A,B,C	89ZOR1323

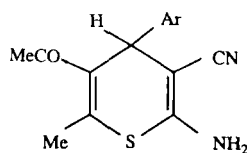
^a X = Cl, MeO.

^b X = Br, Cl, F, Me, MeO, Me₂N, NO₂.

^c X, Y = 2, 4; 2, 5; 3, 4.



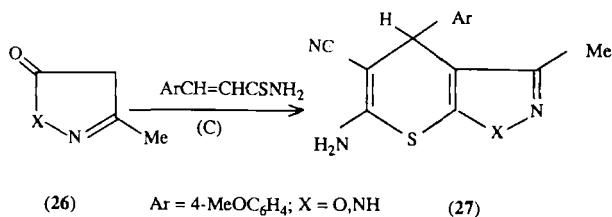
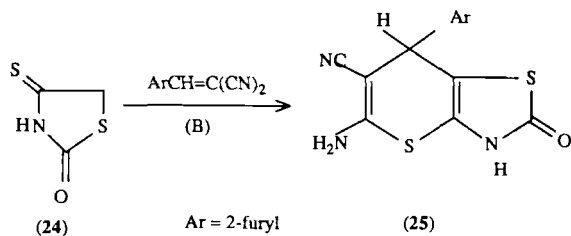
(22)



(23)

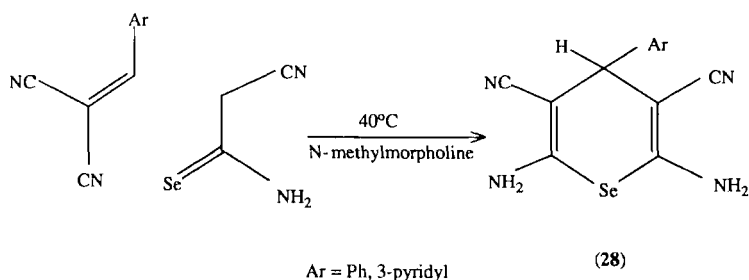
X = H, 4-Br, 4-Cl, 4-Me, 4-MeO

Ar = 4-MeOC₆H₄



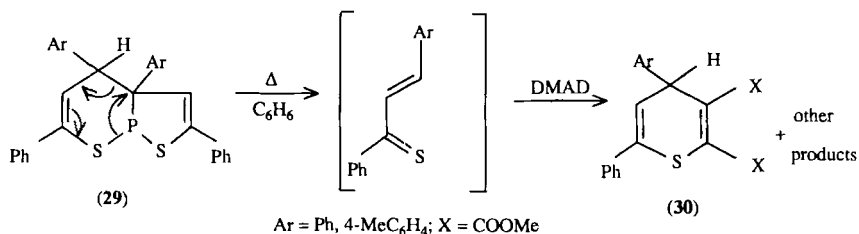
E. SELENOPYRANS FROM SELENOAMIDES

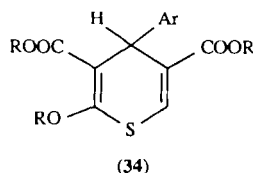
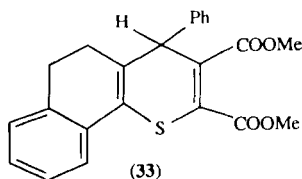
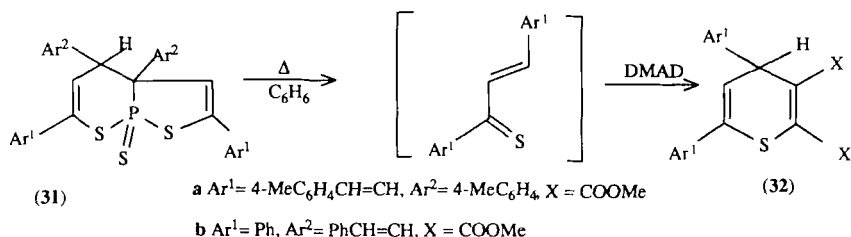
The use of cyanoselenoacetamide instead of its thianalog in procedure B (Scheme 1) afforded expected *4H*-selenopyrans **28** [87ZOB(L)1662; 88UKZ615; 89ZOB(L)881; 90UKZ287]. Further applications of this approach may be expected.



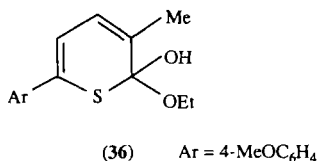
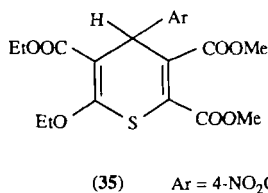
F. THIOPYRANS FROM ACETYLENES

Heterocyclizations of dimethyl acetylenedicarboxylate (DMAD) with α,β -unsaturated thiocarbonyl compounds, the general route to thiopyrans (83ACH145, Section III,F), have been applied to the preparation of *4H*-thiopyrans **30**, **32a**, and **32b** from the enethione precursors **29**, **31a**, and **31b** (86BCJ2047; 88CL717; 92BCJ923). Annulated *4H*-thiopyrans **33** were obtained in the same manner (86BCJ2047). Analogous preparations of derivatives **34** and **35** from thioesters $\text{ArCH}=\text{C}(\text{CO}_2\text{R})\text{CSOR}$ and alkyl acetylenedicarboxylates or DMAD were patented in connection with cardiovascular activities [83GEP(O)3212737]. Some other applications of acetylenic compounds in the heterocyclizations with enamines are discussed in the next section.



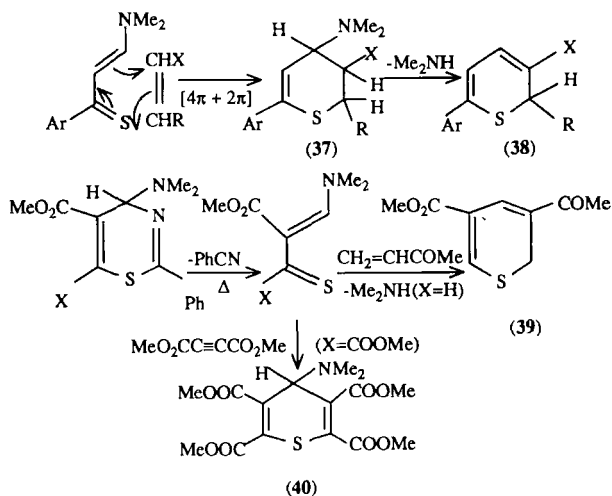


R = Me, Et; Ar = Ph, 2-ClC₆H₄, 3-ClC₆H₄,
 2-CF₃C₆H₄, 3-NO₂C₆H₄,
 4-NO₂C₆H₄, 2,4-Cl₂C₆H₃



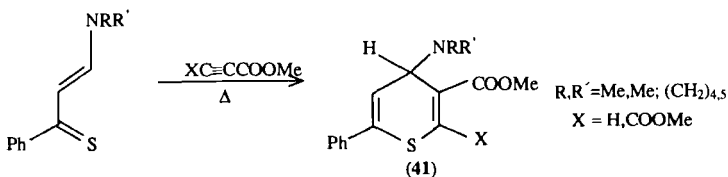
G. THIOPYRANS FROM ENAMINES

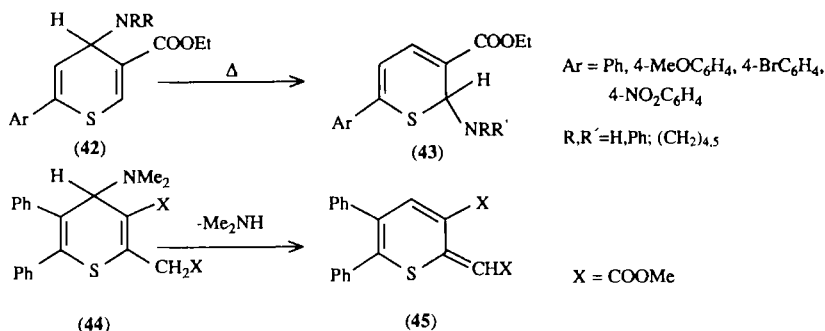
Diels-Alder cycloadditions of enaminothiones with electrophilic dienophiles (83AHC145, section III,G) have been widely used for the preparation of various thiopyran derivatives. In addition to expected 2*H*-thiopyrans, 4*H*-isomers were trapped as intermediates or even as final products. Nitroolefines (90T1951), olefinic carbonyl derivatives [80JH405; 85JOC1545; 92JCS(P1)2603] allenedicarboxylic esters [89JCR(S)300], acetylenecarboxylic esters (80JHC405; 81T3693; 82T1705), and dimethyl acetylenedicarboxylate (81T3693; 82T1705; 85JOC1545) were the dienophiles. An exceptional is unstable hemiacetal **36**, which is considered an intermediate after the reaction of the enithione 4-MeOC₆H₄CSCH=CHN(CH₂CH₂)₂ with the enolate MeCH=C(OLi)OEt (82PS325).



2H-Thiopyrans **38** (Ar = Ph; R = H; X = CO₂Me, CN) have been obtained only by the thermally or photochemically induced cycloaddition–elimination process starting with the olefinic components RCH=CHX (80JHC405). The formation of intermediates **37** (Ar = Ph, 4-ClC₆H₄, 4-MeC₆H₄; R = Ph, 4-MeOC₆H₄, 2-furyl; X = NO₂) was found to be spontaneous and stereospecific (90T1951). The presence of NHAr groups instead of NMe₂ in **37** was found to prohibit the elimination **37** → **38** (90T1951). The starting enaminothione can be generated *in situ* as realized in the preparation of thiopyran **39** (85JOC1545).

The use of acetylenic dienophiles has been observed generally to lead to **4H**-thiopyrans as exemplified for **40** (85JOC1545) and **41** (80JHC405; 81T3693; 82T1705). The thermodynamically more stable 2-amino-**2H**-isomers **43** have been isolated as main products (81T3693; 82T1705) if attempts to synthesize **42** were performed at elevated temperatures. The mechanism of the thermal isomerization **42** → **43** was established (81T3693) using isotopically labeled ethyl acetylenecarboxylate. The 4-thiopyran (**44**) arising after the cyclocondensation of the enethione PhCSC(Ph)=CHNMe₂ with the allenic diester MeO₂CCH=C=CH-CO₂Me was found to be unstable [89JCR(S)300] because of its easy conversion to **45**.





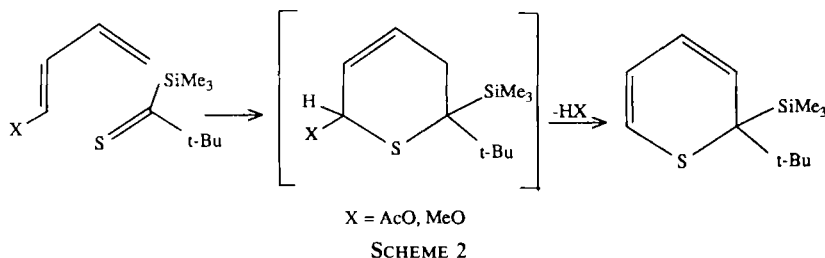
H. THIOPYRANS FROM OTHER ACYCLIC PRECURSORS

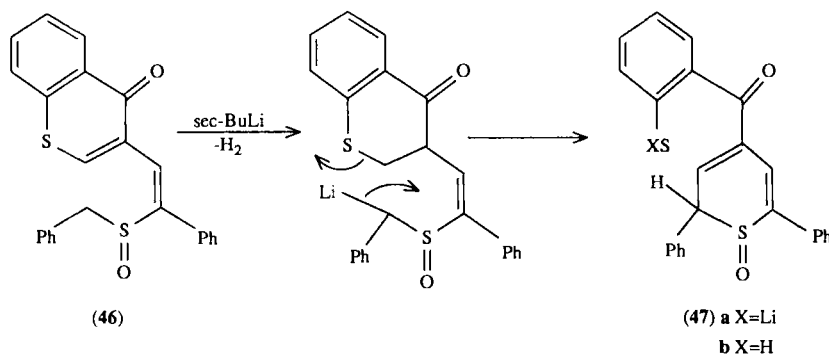
The formation of 2-(*t*-butyl)-2-trimethylsilyl-2*H*-thiopyran has recently been reported from 1-substituted 1,3-butadienes with *t*-BuCSSiMe₃ (92MI1) (see Scheme 2). An unusual product with proposed structure **47b** has been reported (84JOC5143) from benzothiopyrone **46** on reaction with *sec*-butyl lithium (**46** → **47a** → **47b**, Scheme 3) on the basis of spectroscopic data. 6-Methylthio-2*H*-thiopyran was isolated after the flash vacuum thermolysis of more complex starting precursors (93TL2605).

IV. Synthesis from Cyclic Precursors

A. THIOPYRANS FROM THIOPYRYLIUM SALTS

Addition reactions of thiopyrylium salts with nucleophiles (83AHC145, Section IV,B) have widely been used for the preparation of various thiopyrans in the last decade (92MI3). On the other hand, the application of catalytic processes still seems to be rare.

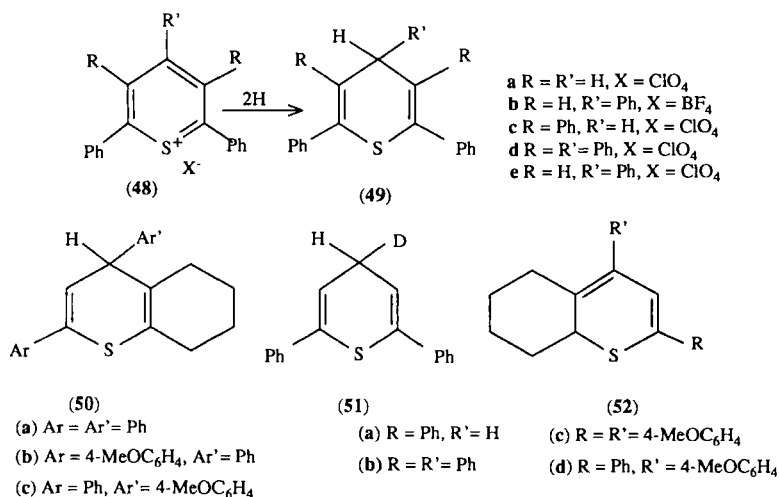


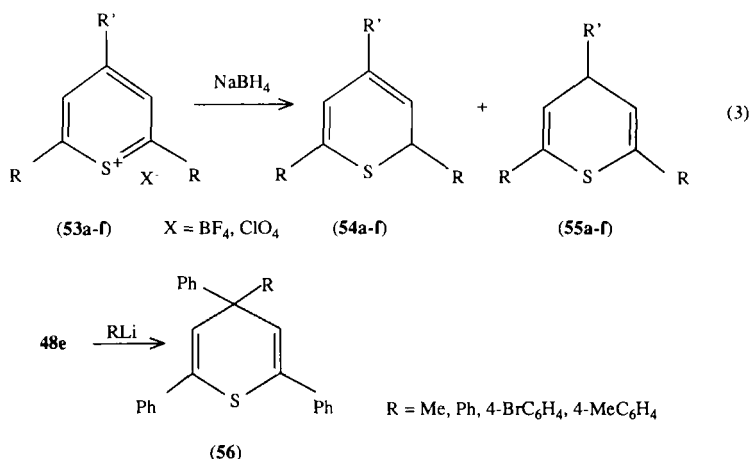


SCHEME 3

1. Reduction

Catalytic hydrogenation of tetrafluoroborate **48b** gave *4H*-thiopyran **49b** (70%) under suitable conditions (10% Pd/C, 30°C , $\text{H}_2/4$ MPa), whereas the analogous formation of **50a** was detected by TLC only (82ZOR2435). The conversions **48** \rightarrow **49** were effectively carried out with complex hydrides, e.g., **48a** \rightarrow **49a** with NaBH_4 and **48a** \rightarrow **51** with NaBD_4 in *i*-PrOH (82JOC680), **48c** \rightarrow **49c** (87%) with LiAlH_4 in ether, and **48d** \rightarrow **49d** with LiBH_4 in THF (84T3539). However, *2H*-thiopyran **52** ($\text{R} = \text{R}' = 4\text{-MeOC}_6\text{H}_4$) was obtained exclusively from the corresponding thiopyrylium trifluoroacetate with LiAlH_4 (87KGS614). Similar reductions of salts **53d**





(X = BF₄) with LiAlH₄ in Et₂O (85CL1119) and **53a–53f** (X = ClO₄) with NaBH₄ in MeOH (91JOC1674) were observed to proceed less regioselectively giving both isomeric thiopyrans **54a–54f** and **55a–55f**, Eq. (3), in relative yields shown in Table II.

Several thiopyrylium salts were reduced electrochemically (84KGS318; 86NJC345; 88MI2; 90KGS1480; 91KGS47) or with zinc (86NJC345; 90KGS1480; 91KGS47) to the corresponding easily recombining radicals but these procedures have not yet been explored preparatively. Hydrogen transfer between 2,4,6-trisubstituted thiopyrylium salts and 4*H*-thiopyrans is discussed in Section D,2.

TABLE II
ISOMERIC THIOPYRANS FORMED ACCORDING TO EQ. (3)^a

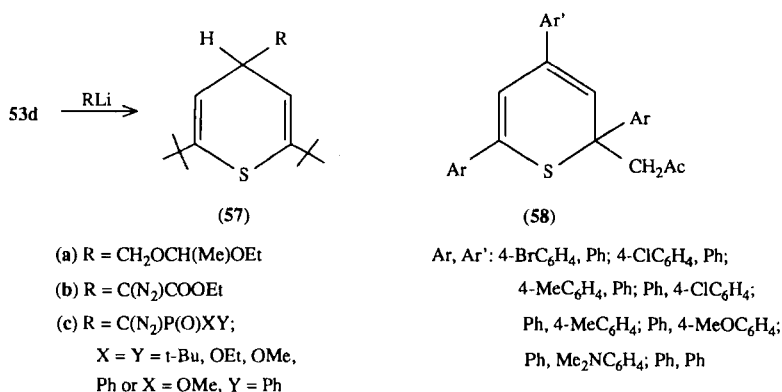
Salt	R	R'	2 <i>H</i> (54) : 4 <i>H</i> (55)	<i>K</i> _{eq} ^b	(°C)
53a	Ph	H	0 : 100	0.16	(25)
53b	Ph	Ph	31 : 69	7.1	(25)
53c	Ph	<i>t</i> -Bu	4 : 96	0.24	(25)
53d	<i>t</i> -Bu	H	9 : 91	1.8	(100)
53e	<i>t</i> -Bu	Ph	91 : 9	36	(100)
53f	<i>t</i> -Bu	<i>t</i> -Bu	31 : 69	4.2	(100)

^a According to Doddi and Ercolani (91JOC1674).

^b Equilibrium constants in CDCl₃.

2. Reactions with C-Nucleophiles and Reductive C-Substitution

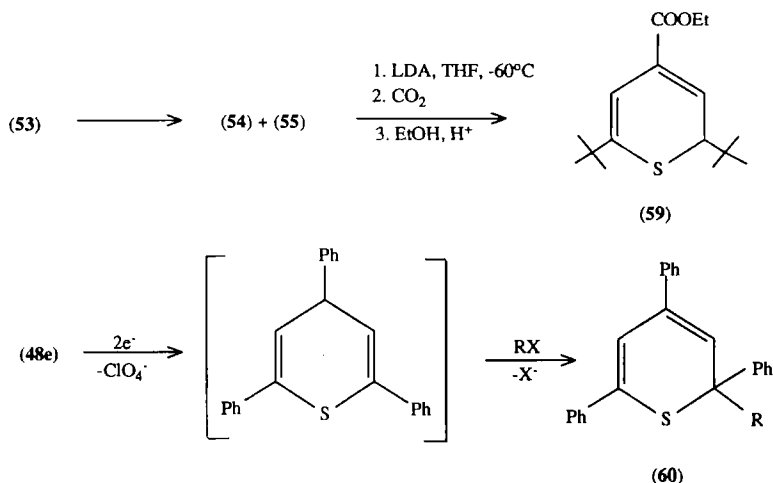
Two principle approaches from thiopyrylium salts to thiopyrans accompanied by C-substitution have been found, e.g., the one-step additions of C-nucleophiles or the two-step procedures involving primary conversions of the salts to nucleophilic intermediates followed by attacks with appropriate electrophiles.



The first approach was used for the preparation of 2,4,4,6-tetrasubstituted 4*H*-thiopyrans **56** from perchlorate **48e** with RLi [91JCS(P2)2061]. Analogously, 4*H*-thiopyrans **57a** and **57b** were reported to be obtained from salt **53d** with reagents LiCH₂OCH(Me)OEt (82TL3195) or LiC(N₂)-CO₂Et (82CL1843). The use of the latter Li compound did not lead, however, to identifiable thiopyrans in another case (85CL1119). On the other hand, phosphorus 4*H*-thiopyran derivatives **57c** were easily prepared using HC(N₂)P(O)XY-Et₃N mixtures at -78°C (85S569, 85T811). The use of 2-thienylmagnesium bromide for the preparation of an annulated 4*H*-thiopyran from a corresponding thiopyrylium salt (91KGS900) is described in Section V,A,1.

A general preparation of 2-acetonyl-2,4,6-triaryl-2*H*-thiopyrans **58** was discovered in the reaction of corresponding 2,4,6-triarylthiopyrylium perchlorates with ethanolic acetone catalyzed with various dialkylammonium salts (86GEP235455, 86JPR573). This preparative procedure was successfully extended to cyclohexane- and cyclopentane-1,2-diones as the carbonyl components (89JPR853; 90GEP280324). The action of bases on thiopyrylium salts may caused their dimerization to thiopyranyl derivatives under suitable conditions (89KGS479).

The second approach has been applied in two versions. The chemical version (85CL1119) consists in the lithiation of mixture **54d** and **55d**,



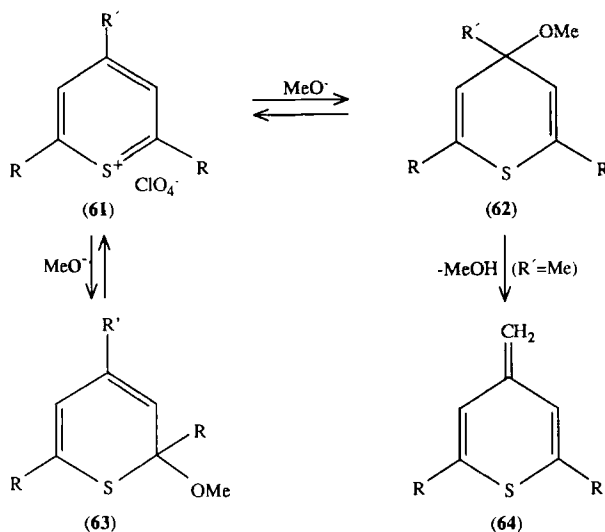
Eq. (3), with lithium diisopropylamide (LDA) to a lithiospecies and in its subsequent reaction with CO_2 affording via the corresponding 4-carboxylic acid its ethyl ester **59**. In the alternative version perchlorate **48e** is electrochemically reduced in acetonitrile to an anionic species that was converted either to a 3 : 1 mixture of isomers **56** ($\text{R} = t\text{-Bu}$) and **60** or to 4*H*-thiopyran **56** ($\text{R} = \text{PhCH}_2$) with $t\text{-BuI}$ or PhCH_2Br , respectively (90ACS524). The kinetics of the benzylation procedure was followed by cyclic voltammetry [88ACS(B)269].

3. Reactions with Oxygen and Sulfur Nucleophiles

The reactions of methanolic sodium methoxide with 2,4,6-triarylthiopyrylium perchlorates **61** have been subjected to many experimental investigations resulting in the chemical picture shown in Scheme 4.

The preparative exploration of such transformations was successful only in a series of 2,4,6-triaryl-2*H*-thiopyrans **63** ($\text{Ar} = \text{Ph}$, 4- BrC_6H_4 , 4- ClC_6H_4 ; $\text{Ar}' = \text{Ph}$, 4- BrC_6H_4 , 4- ClC_6H_4 , 4- MeC_6H_4 , 4- MeOC_6H_4 , 4- $\text{Me}_2\text{NC}_6\text{H}_4$), which were isolated after corresponding salts **61** were heated with MeONa – MeOH mixtures (83ZC333; 86JPR373).

Kinetic studies of the MeONa addition to salts **61** ($\text{R} = t\text{-Bu}$; $\text{R}' = \text{H}$, Me , and $\text{R} = \text{Ph}$; $\text{R}' = \text{H}$, MeO) at -40°C have shown the reaction to be kinetically controlled and to lead exclusively to 4*H*-thiopyrans **62** [86JCS(P2)271; 87JCS(P2)1427]. In other cases ($\text{R} = t\text{-Bu}$) mixtures of both 4*H*- and 2*H*-isomers **62** and **63** ($\text{R}' = \text{Ph}$, 3- ClC_6H_4 , 4- ClC_6H_4 , 4- MeC_6H_4 , 4- MeOC_6H_4 , 4- $\text{Me}_2\text{NC}_6\text{H}_4$) were formed, but the 2*H*-isomer **63** ($\text{R}' = 4\text{-O}_2\text{NC}_6\text{H}_4$) was only formed (86JA3409).



SCHEME 4

Thermodynamic investigations established the equilibrium composition of the thiopyran isomers at 25 to 30°C [86JA3409; 86JCS(P2)271; 87JCS(P2)1427, 89JCS(P2)1393]. Thus, there resulted only *2H*-thiopyrans **63** ($\text{R} = t\text{-Bu, Ph}$) when R' was phenyl, or a 3- or 4-substituted phenyl group [86JA3409, 86JCS(P2)271] and only *4H*-thiopyran **62** when $\text{R} = \text{Ph}$ and $\text{R}' = \text{MeO}$ [86JCS(P2)271]. Mixtures of both isomers **62** and **63** arose in other cases [86JCS(P2)271; 87JCS(P2)1427]. 4-Methyl-4*H*-thiopyrans **62** ($\text{R} = t\text{-Bu, Ph}$) exhibited an exceptional behavior, being irreversibly transformed to 4-methylene derivatives **64** according to Scheme 4 [89JCS(P2)1393].

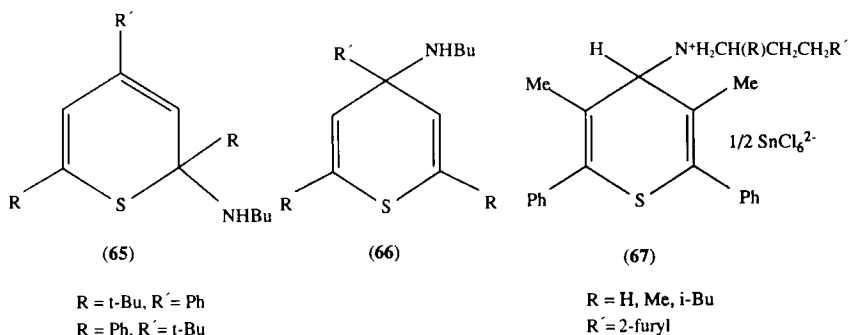
The equilibria between *2H*-thiopyrans **63** ($\text{R} = 4\text{-MeOC}_6\text{H}_4$; $\text{R}' = \text{Ph, 4-MeOC}_6\text{H}_4$) and their corresponding thiopyrylium salts were utilized to replace ClO_4^- , BF_4^- , Cl^- , and CF_3CO_2^- ions by other counterions in the patent literature (88URP1447824).

No addition products with S-nucleophiles have yet been reported except for the reaction of 2-methylthio-4,6-diphenylthiopyrylium iodide with sodium thiophenolate involving a *2H*-thiopyran intermediate (86S916).

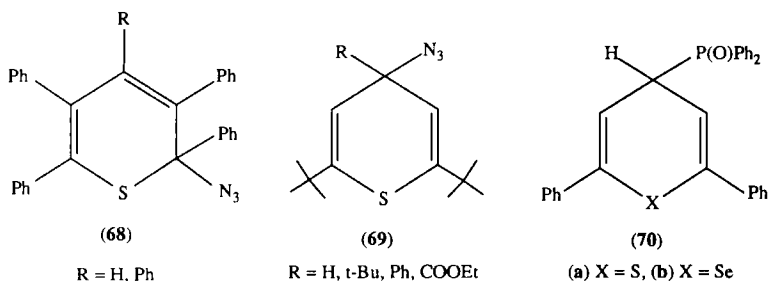
4. Reactions with Nitrogen and Phosphorus Nucleophiles

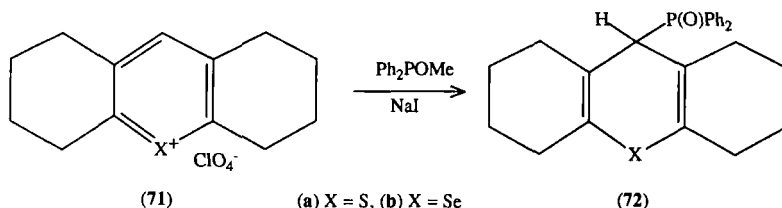
Any preparative utilization of the addition reactions of thiopyrylium salts with amines appears to be significantly dependent on the nucleophili-

ties of the reagents in appropriate solvents. Thus, the $\text{BuNH}_2/\text{DMSO}$ reagent at 25°C was reported to form mixtures **65** + **66** under kinetic control and finally the thermodynamically more stable $2H$ -isomers **65** in equilibrium with the starting perchlorates **61** (89G205). The conclusions correspond to some earlier thermodynamic and kinetic studies of the reactions of **48e** with various amines (82JOC3496, 84JA7082, 84JOC1806). The $2H$ -thiopyrans adducts from **48** ($\text{R} = \text{H}, \text{Me}$; $\text{R}' = \text{Ph}, 4\text{-BrC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4$, and $4\text{-MeOC}_6\text{H}_4$) and Me_2NH or morpholine were prepared (83ZC144; 86JPR567) and patented as dye intermediates (84GEP212964). On the other hand, thiopyran salts **67** were prepared from **48** ($\text{R} = \text{Me}$, $\text{R}' = \text{H}$, $\text{X} = 1/2 \text{SnCl}_6$) with primary amines and tested for antiviral and antibacterial activities (87KFZ696).



Some doubts have arisen in connection with the regioselectivity of nucleophilic attack on thiopyrylium salts by sodium azide. Whereas $2H$ -thiopyrans **68** were isolated after the reactions of the reagent with salts **48c** and **48d** (84T3539), analogous primary adducts from **61** ($\text{R} = t\text{-Bu}$, $\text{R}' = \text{H}, t\text{-Bu}, \text{Ph}$ or CO_2Et) were thought to be $4H$ -thiopyrans **69** [89PS(43)243]. Several products were observed to be unstable [84T3539, 84T3559; 89PS(43)243].

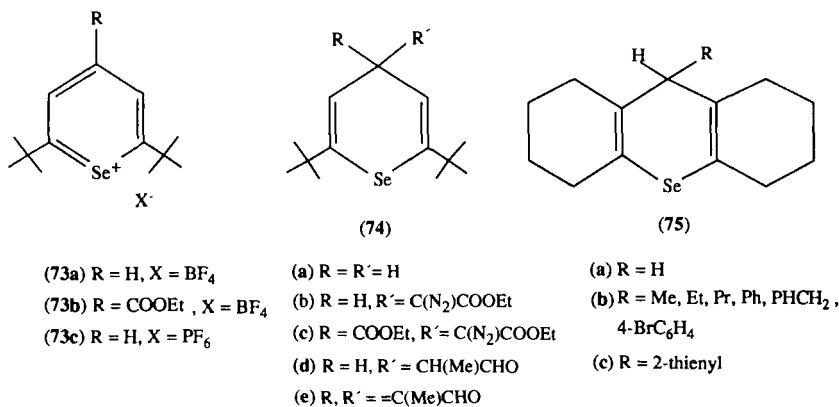




The addition of diphenylmethoxyphosphane to 2,6-diphenylthiopyrylium perchlorate (**48a**) in the presence of sodium iodide in acetonitrile was found to lead to isolable 4*H*-thiopyran **70a**. The transformation **71a** → **72a** proceeded analogously [90ZOB(L)1012].

B. SELENOPYRANS FROM SELENOPYRYLIUM SALTS

This type of selenopyran synthesis seems to paraphrase the procedures with thia-analogs (Section IV,A). Thus, tetrafluoroborate **73a** reacted with LiAlH_4 to give the expected 4*H*-selenopyran **74a** (90AG450) and the analogous conversion **71b** → **75a** was accomplished with the same reagent as well as with NaBH_4 (82MI2). A number of 4-substituted 4*H*-selenopyrans **75b** were also prepared from **71b** but with corresponding Grignard reagents (82MI2; 91KGS47). Other additions of C-nucleophiles to salts **73a** and **73b** were achieved with $\text{LiC}(\text{N}_2)\text{CO}_2\text{Et}$ affording the expected 4*H*-selenopyrans **74b** and **74c**, but in low yields, 16 and 21%, respectively (90AG450).



Reversible additions of sodium methoxide to certain 2,4,6-triarylselenopyrylium salts were reported to lead to unstable 2-methoxy-2*H*-selenopyran intermediates, which could be reconverted into the starting

cations with various counteranions (88URP1447824). The preparation of 4*H*-selenopyran **70b** from 2,6-diphenylselenopyrylium perchlorate as well as the conversion of **71b** \rightarrow **72b** was found to be perfect by analogus to **48a** \rightarrow **70a** and **71a** \rightarrow **72a** in the thia-series [90ZOB(L)1012].

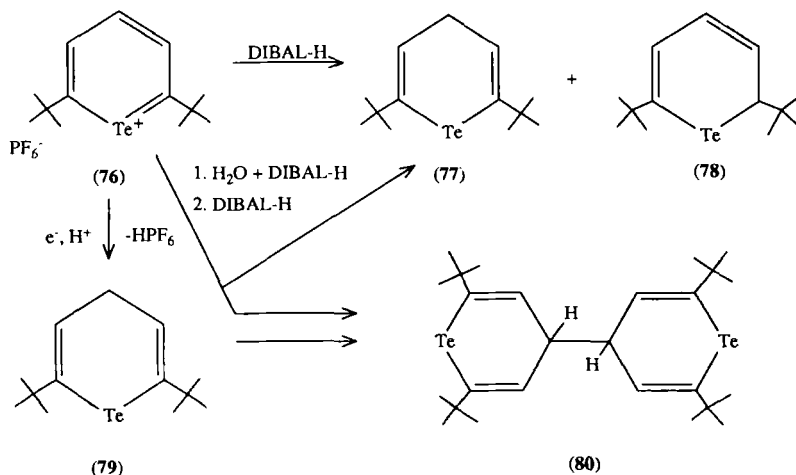
A mixture of 4*H*-selenopyranyl aldehyde **74d** (50%) and related 4*H*-selenopyranylidene derivative **74e** (35%) was obtained after treatment of hexafluorophosphate **73c** with $\text{MeCH}=\text{CHNPr}_2$ generated *in situ* from Pr_3N and I_2 in EtCN at elevated temperature (84JOC2676).

C. TELUROPYRANS FROM TELUROPYRYLIUM SALTS

Detty published the first example of the titled approach in his pioneering work on teluopyrans (88MI1). The hexafluorophosphate **76** was reduced with diisobutyl aluminium hydride (DIBAL-H) to a 93 : 7 mixture of isomeric teluopyrans **77** and **78** accompanied by traces (ca. 1%) of the dimeric product **80**. The latter was also obtained after the electrochemical reduction of **76** via radicals **79** or by a modification of the reduction with DIBAL-H (Scheme 5).

D. THIOPYRANS FROM DIHYDROTHIOPYRANS AND TETRAHYDROTHIOPYRANS

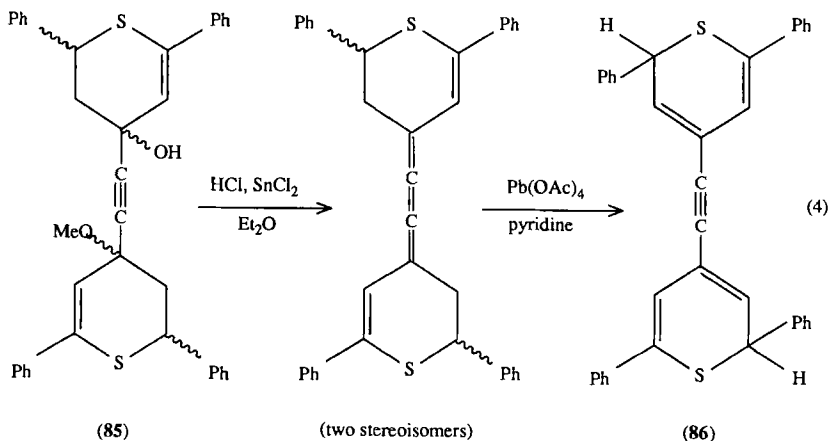
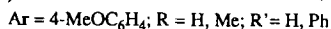
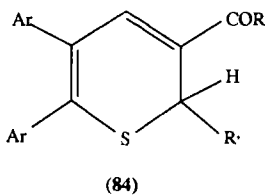
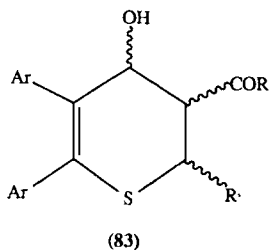
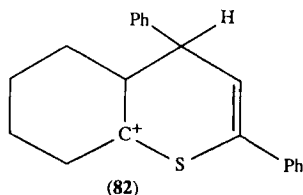
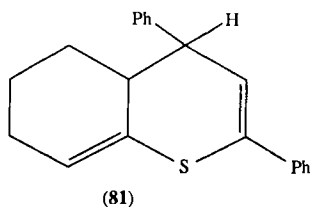
This type of transformation had been recognized early to produce a variety of thiopyrans (83AHC145, Section IV.E) and has been widely



SCHEME 5

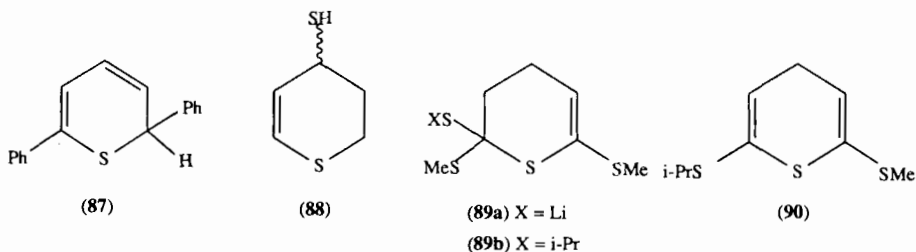
applied in the last decade. The isomerization of **81** with hydrogen chloride is a simple route to 4*H*-thiopyran **50a** via cation **82** as proved by a deuterium labeled reagent (81KGS1342).

Dihydrothiopyrans bearing a hydroxy group or another readily eliminating substituent are usual starting or intermediate compounds, as mentioned in sections III,D and III,G in the cases of **19** and **37**. 4-Hydroxy-3,4-dihydro-2*H*-thiopyrans **83** obtained by the thioenolate procedure (Section III,C) were quantitatively dehydrated with potassium hydroxide to 2*H*-thiopyrans **84** (87S456). Acetylenic bis-(4-hydroxy-2,3-dihydro-4*H*-thiopyran) derivative **85** was transformed to the corresponding bis-2*H*-thiopyran **86** via stereoisomeric allenic intermediates (81CC1143), according

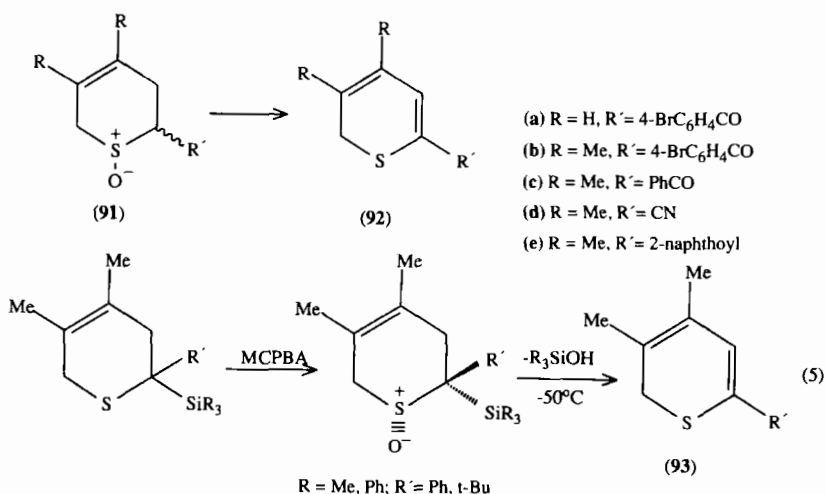


to Eq. (4). The oxidative dehydration of 2,6-diphenyl-1-thiacyclohexan-4-ol with *N*-chlorosuccinimide (NCSI) was found to afford 2,6-diphenyl-2*H*-thiopyran (**87**) in the presence of molecular sieves (82JOC680).

4-Hydrosulfido-2,3-dihydro-4*H*-thiopyran (**88**) was reported to be an intermediate in the reaction of 2,6-dithiabicyclo[3,1,1]heptane with phenylmethanethiol leading to unsubstituted 2*H*-thiopyran (**1**) together with other products (89JOC5821). Similar elimination of PhSH has been used for the synthesis of more complex 2*H*-thiopyrans (88CL1029, 90BCJ2540, 92BCJ2056, 93BCJ2124). The formation of 4*H*-thiopyran derivative **90** was observed from the lithio intermediate **89a** (from dimethyl tetrathioglutarate with LDA) in attempts at alkylations of **89a** to **89b** with isopropyl bromide (88LA933).

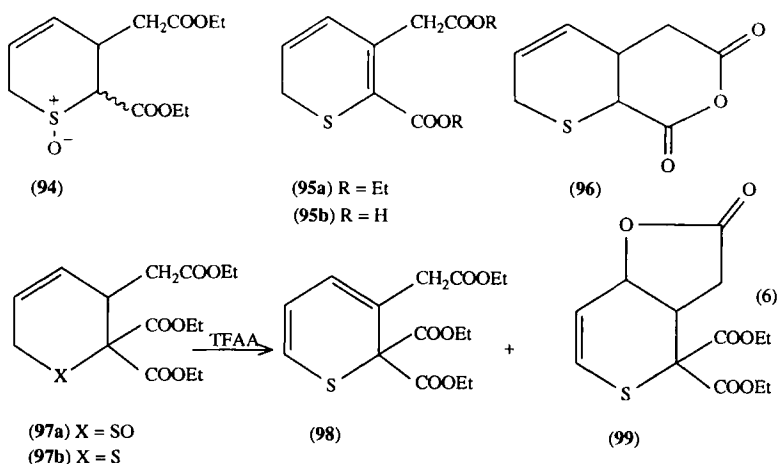


The dehydration of 5,6-dihydro-2*H*-thiopyran-*S*-oxides involving the Pummerer rearrangement has been explored as a general approach to 2*H*-thiopyrans. Thus, the acid-catalyzed transformations **91a-e** \rightarrow **92a-e** achieved in boiling toluene or xylene solutions have been described (85JOC2930; 90TL115) in addition to further substituent R' variability (85JOC2930). Analogously, 6-substituted 3,4-dimethyl-2*H*-thiopyrans (**93**)



were obtained from the appropriate 2-(trisubstituted)silyl dihydroderivatives with *m*-chloroperbenzoic acid (MCPBA) via unstable *cis*-*S*-oxides ($R' = t\text{-Bu}$) [87JCS(P1)2643; 89JCS(P1)2083] according to Eq. (5). The *trans*-*S*-oxide ($R' = t\text{-Bu}$) was found to be incapable of rearrangement to **93** probably due to the rigidity of its heterocycle [89JCS(P1)2083].

The regular regioselectivity of the rearrangement was also observed in the reactions of diester **94** with trifluoroacetic anhydride (TFAA) leading to **95a** or of cycloanhydride **96** with NCSI affording dicarboxylic acid **95b**. On the other hand, triester **97a** was found to behave toward TFAA anomalously, giving mixtures of thiopyran **98** and lactonic dihydrothiopyran **99**, Eq. (6), in variable ratios depending on the reaction conditions. Similar products were obtained after the reaction of thiopyran **97b** with NCSI [88JCS(P1)663].

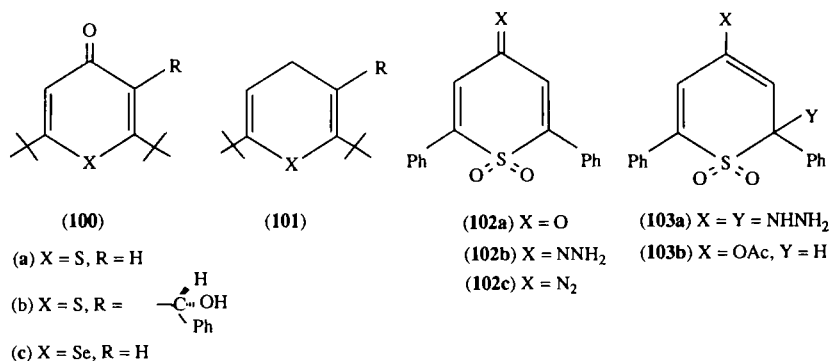


Recently, the Pummerer rearrangement has been employed also in the *2H*-selenopyran synthesis (93CC577).

E. THIOPYRANS FROM THIOPYRONES AND SIMILAR CYCLIC KETONES

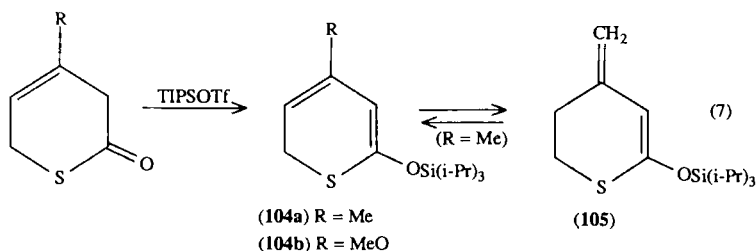
These approaches to thiopyrans, based on carbonyl group transformations, have been developed mainly in the last decade.

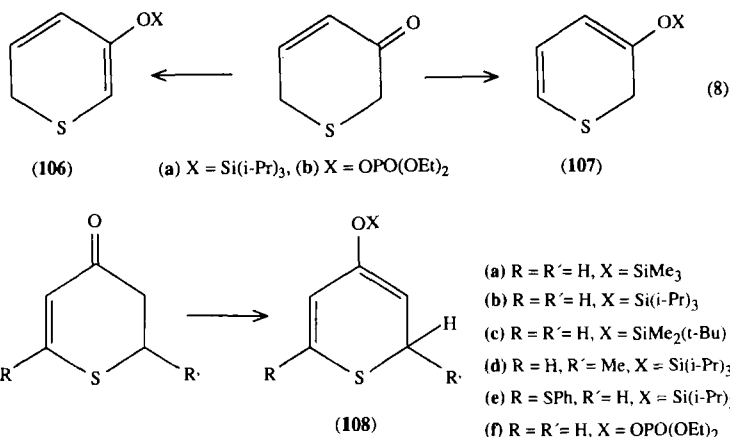
The reduction of 4-thiopyrones **100a** and **100b** with DIBAL-H was found to lead to 4*H*-thiopyrans **101a** and **101b**, e.g., with complete elimination of oxygen functionalities from the molecules (88M11). The carbonyl group in sulfone **102a** was found to react with MeMgI and $(\text{MeO})_2\text{POCH}_2\text{Li}$ to corresponding 4-hydroxy-4*H*-thiopyrans (86JOC3282). *S,S*-dioxide **102a**



and its heteroanalogs **102b** and **102c** were converted, on the other hand, to 2*H*-thiopyran systems. Thus, 2,4-bis-hydrazine **103a** was formed from **102a** via hydrazone **102b** with two equivalents of hydrazine itself at enhanced temperature. Analogously, 2*H*-thiopyran-*S,S*-dioxide **103b** was obtained by heating **102c** in acetic acid (86JOC3551).

Dihydrothiopyrones are usually the prevailing tautomers of hydroxythiopyrans. The preparations of the latter consist therefore in fixation of the thiopyran structures by enol ether bonds or by other substitution patterns preferring the enol form. Effective routes enabling the enol ether type of fixation were recognized in silylation with a Me₃SiCl–ZnCl₂ complex (TMSCL) or triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) or *t*-butyl dimethylsilyl trifluoromethanesulfonate (TBMSOTf) in the Et₃N–CH₂Cl₂ solvent (83YZ1096; 90TL845; 91CJC1487) or TIPSOTf with LDA or in the phosphorylation with LDA and diethyl chlorophosphate (91CJC1487). Thus, 4-substituted 3,6-dihydro-2*H*-thiopyrones gave 2*H*-thiopyrans **104a** and **104b** by subsequent reactions, Eq.(7), with LDA TIPSOTf (90TL845; 91CJC1487) but in the case of **104a** only its difficulty separable mixture with exocyclic isomer **105** (91CJC1487). Surprisingly, 2,3-dihydro-6*H*-thiopyran-3-one with TIPSOTf or ClPO(OEt)₂ underwent two competitive reactions, Eq.(8), to the expected 5-substituted 2*H*-thiopyrans **106a** and **106b** in addition to their 3-substituted isomers **107a** and **107b**, respectively. The ratios of **106**:**107** were found to depend on the reaction conditions. The analogous reaction paths from tetrahydro-



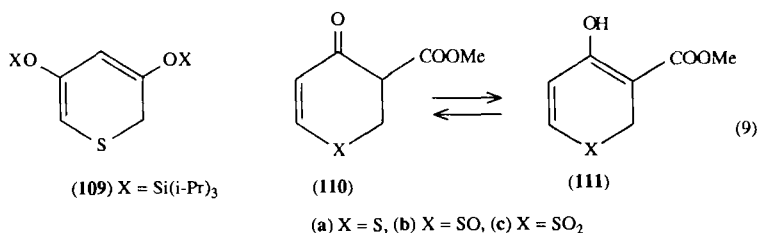


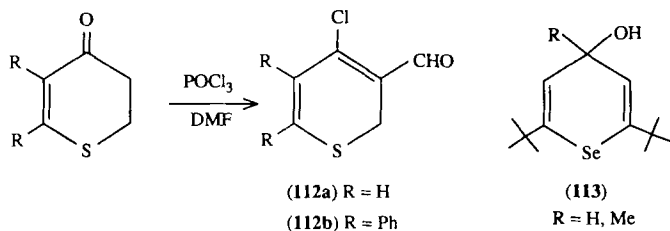
4*H*-thiopyran-3,5-dione and TIPSOTF led comprehensibly to one 3,5-disubstituted 2*H*-thiopyran **109** (91CJC1487).

A high regioselectivity was observed for both silylation and phosphorylation of various 2,3-dihydro-4*H*-thiopyrones, affording 2*H*-thiopyrans **108a–f** in almost quantitative yields (83YZ1096; 90TL845; 91CJC1487).

The possibility of obtaining 2*H*-thiopyranoic hydroxy esters **111** from keto esters **110** was found to be strongly limited by the character of the heteroatomic group X influencing the tautomerism shown in Eq.(9). Whereas for the pairs of thia-isomers **110a** and **111a** as well as sulfoxides **110b** and **111b** the oxo-tautomers **110** were observed to be entirely prevailing [84JCS(P1)2549; 86JCS(P2)1887], in the case of sulfones **110c** and **111c** the latter was the only detectable species in the solid and solution (CDCl₃) states [86JCS(P2)1887]. Consequently, mild S-oxidation of **110a** with MCPBA at 20°C in CH₂Cl₂ yielded only **111c** (22%) and **110b** (12%).

A somewhat more promising approach to 2*H*-thiopyran-3-carboxaldehydes seems to be the Vilsmeier–Haack reaction with 2,3-dihydro-4*H*-thiopyrones affording the chloroaldehydes **112a** (90SC2749, 90TL5227; 91T1303) and **112b** in 30 and 58% yields, respectively.



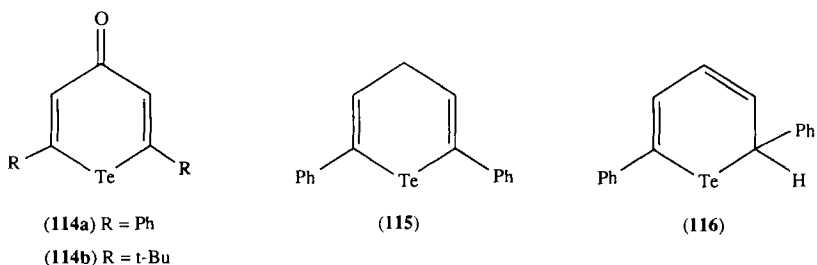


F. SELENOPYRANS FROM SELENOPYRONES

4-Hydroxy-4*H*-selenopyrans **113** have been reported to be air-sensitive intermediates in the transformations of **100c** to salts **73a** and **73** (R = Me) by successive action of lithium aluminium hydride or methyllithium and then tetrafluoroboric acid (90AG450). 4*H*-Selenopyranone **100c** was reduced to 4*H*-selenopyran **101c** with DIBAL-H (88MI1).

G. TELUOPYRANS FROM TELUOPYRONES

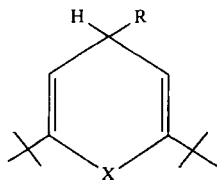
The relatively stable 2,6-diphenyl-4*H*-teluopyrone (**114a**) was reduced to 4*H*-teluopyran **115** (95%) accompanied by a small amount of its 2*H*-isomer **116** (5%) with DIBAL-H. The same reagent gave a similar mixture of **77** (93%) and **78** (7%) from 2,6-di(*t*-butyl) derivative **114b** as well as dimeric product **80** in 29% yield (88MI1).



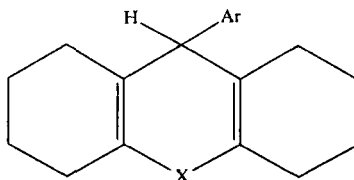
H. THIOPYRANS AND SELENOPYRANS FROM PYRANS

4*H*-Pyrans have rarely been transformed to their thia- and seleno-analogs probably because of more advantageous alternative syntheses from 1,5-dicarbonyl precursors (Sections III,A and III,B). A relatively lower yield of 2,4,6-trisubstituted 4*H*-thiopyran **117a** (19%) was obtained from a mixture of 4*H*-pyrans **117b** and **117c** (87CCC1305) with a gaseous

HCl-H₂S. The preparations of 4*H*-thiopyran **118a** and 4*H*-selenopyrans **13b** and **13e** (with HCl-H₂Se) from **118b** and probably **118c** have also been reported (91KGS51, 91KGS900). The conversion **10** → **11** (Ar¹ = Ar² = Ar³ = Ph) was more effectively accomplished with P₄S₁₀ in xylene [92JCS(P2)1301].

(117a) R = *t*-Bu, X = S(117b) R = *t*-Bu, X = O

(117c) R = H, X = O

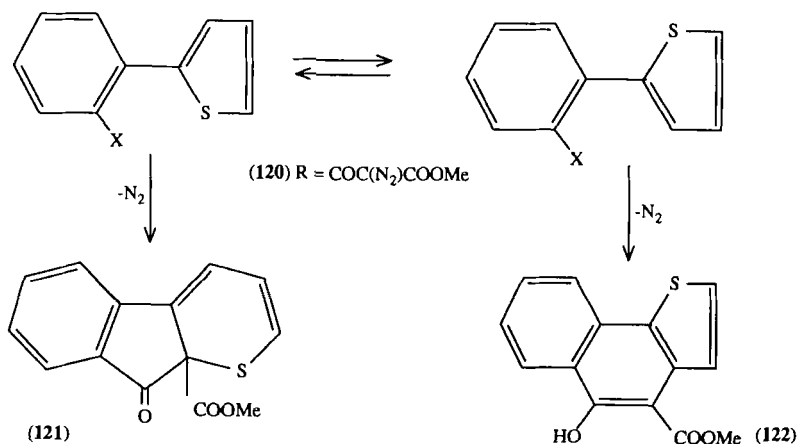
(118a) Ar = 4-MeOC₆H₄, X = S(118b) Ar = 4-MeOC₆H₄, X = O

(118c) Ar = Ph, X = O

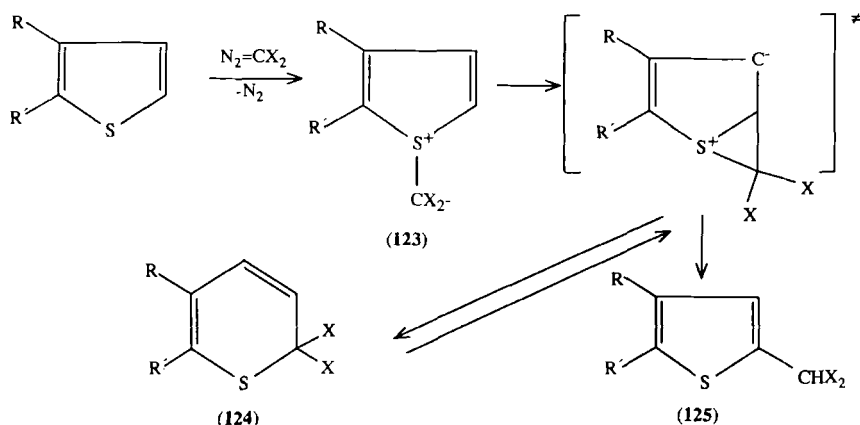
4*H*-Thiopyrans **50a-c** were also obtained from the corresponding 2-methoxy-2,3-dihydropyrans by treatment with a H₂S-HCl-Ac₂O-AcOH mixture (86KGS28).

I. THIOPYRANS FROM THIOPHENES

The intramolecular origin of the 2*H*-thiopyran **121** together with its expected isomer **122** was discovered by treatment of the thiophene derivative **120** with Rh₂(OAc)₄ (84CC208) (see Scheme 6). More detailed investigations of the intermolecular version of the transformation (Stevenson



SCHEME 6



SCHEME 7

rearrangement) giving isomeric products **124** and **125** have proved that the process proceeds via isolable thiophene ylides **123** and three-membered cyclic transition states according to Scheme 7 [85CC1590; 88JCS(P1)803, 88JCS(P1)809]. The CO photoextrusion from some 2,3-dihydrothiophen-2-ones gave mixtures containing 2*H*-thiopyrans (92CB2311).

V. Reactions

A. OXIDATION

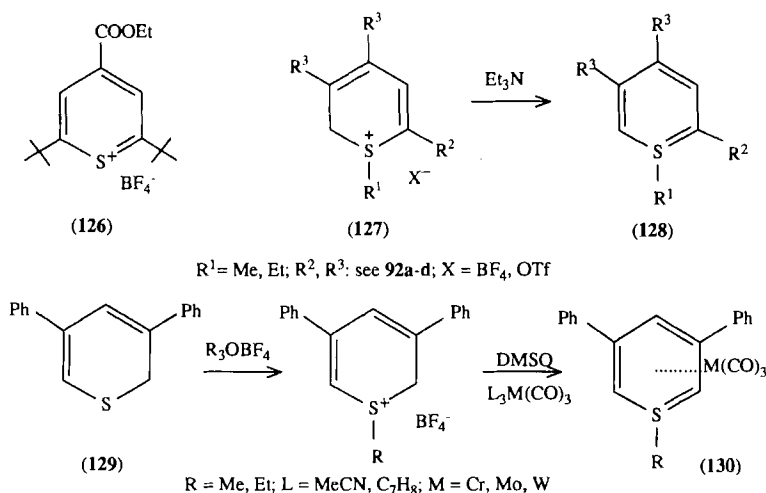
Further examples of the transformations of heteropyrans to heteropyrylium salts (92MI3) as well as the S-oxygenation of thiopyrans with hydrogen peroxide have been described.

1. Aromatizations of Thiopyrans to Thiopyrylium Salts

The agents used for oxidative aromatization of various thiopyrans were air-dioxygen (81KFZ38; 83KGS1689; 91KGS181), trityl tetrafluoroborate (81CC1143; 85CL1119), 3,4-di-(*t*-butyl)-1,2-benzoquinone (DTBQ) (91KGS51), hydrogen peroxide (85KGS1042), and a rotating platinum disk electrode (84KGS318).

The aromatization of nonquaternized 2*H*-thiopyrans seems to be still exceptional as the conversions **59** → **126** or **86** to appropriate bis-thiopyrylium salt with Ph_3CBF_4 (85CL1119; 81CC1143). On the other

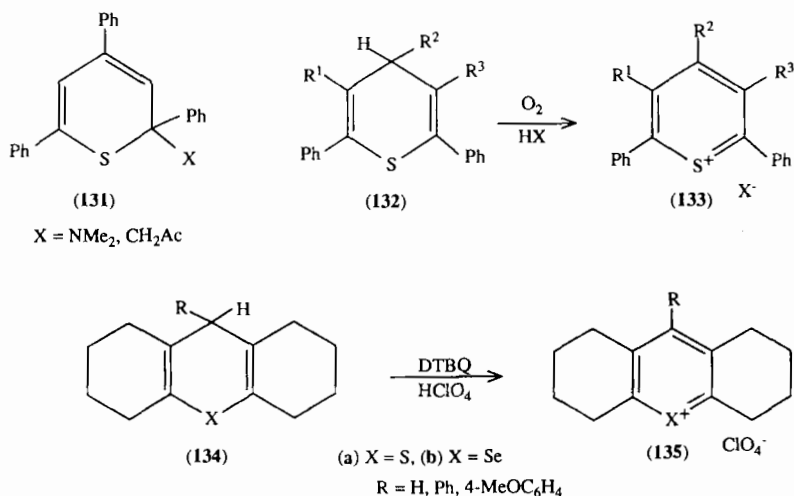
hand, 2*H*-thiopyran systems after their S-alkylation are easily capable of aromatization. Thus, thiabenzenes **128** were reported to be obtained from the salts **127** prepared with R^1I -AgBF₄, $(R^1O)_2CHOBf_4$, or MeOTf reagents (90TL115). Analogously, 3,5-diphenyl-2*H*-thiopyran (**129**) was repeatedly aromatized to unstable 1-substituted 3,5-diphenylthiabenzenes isolated as their metal complexes **130** (81AG304; 82CB1775).



Although the aromatizations of 2-methoxy-2*H*-thiopyran derivative **63** (R = R' = Ph, 83ZC333; 86JPR373) or similar compounds **131** (86JPR567, 86JPR573) to perchlorate **48e** or appropriate chloride with some acidic reagents resemble the above-mentioned conversions, they are not oxidation processes.

A number of examples of 4*H*-thiopyran aromatizations to thiopyrylium salts evidently involves the 4-hydrogen transfer from the starting heterocycles associated with their reducing properties. In fact, many 4*H*-thiopyrans were observed to be air sensitive especially in acidic media as illustrated by the transformations **132** \rightarrow **133** (R¹, R², R³ = Me, Me, Me; Me, Me, Et; Me, Me, Ph; Me, Ph, H; X = ClO₄)₄, 81KFZ38). The reaction mechanism involving radical cation intermediates is discussed in connection with the detection of methane and carbon dioxide in resulting mixtures (83KGS1689). Analogous electrochemical conversions of **132** to **133** (R¹ = R³ = H, Ph; R² = Ph; X = ClO₄) were interpreted to proceed by the ECE mechanism (84KGS318). Further aromatizations **134a** \rightarrow **135a** were accomplished with quinone-DTBQ (91KGS51) or by heating with CF₃CO₂H under elimination of substituents from position 4 (91KGS900).

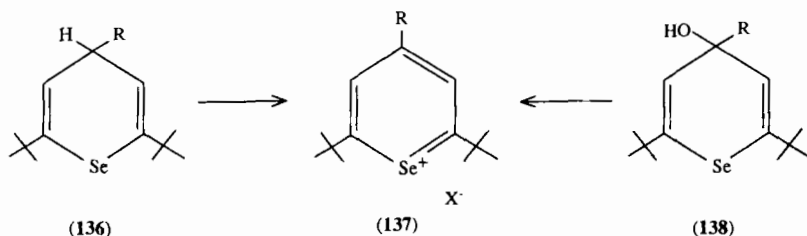
4*H*-Thiopyran **134a** (R = 2-thienyl) was prepared from perchlorate **135** (R = H) with 2-thienylmagnesium bromide (91KGS900).



2. Aromatizations of Selenopyrans to Selenopyrylium Salts

The transformations **136** \rightarrow **137** (R = H, X = PF₆) accomplished by heating with HPF₆ in acetic acid (88MI1) and **136** (R = CO₂Et) \rightarrow **73b** with Ph₃CBF₄ at 20°C (90AG450) belong to oxidative-dehydrogenation processes. On the other hand, similar conversions of unstable 4-hydroxy-4*H*-selenopyrans **138** (R = H, Me) arising from 2,6-di-(*t*-butyl)-4*H*-selenopyrone with LiAlH₄ or MeLi (90AG450) and affording tetrafluoroborates **137** (R = H, Me), after additional treatment with HBF₄, are evidently not oxidations.

Annulated 4*H*-selenopyrans **134b** (R = 4-MeOC₆H₄, 2-thienyl) were found to split off the 4-substituents on heating with CF₃CO₂H (91KGS900).

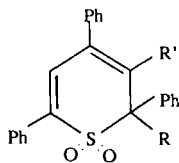
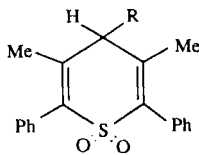
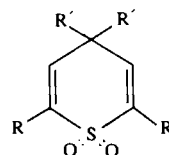
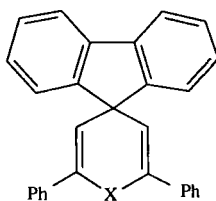
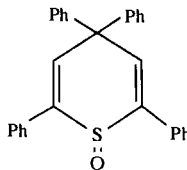


3. Aromatizations of Teluopyrans to Teluopyrylium Salts

4*H*-Teluopyran **77** was converted to hexafluorophosphate **76** by heating with a HPF_6 -AcOH mixture in an inert atmosphere. The same product was obtained by the electrochemical oxidation of the dimeric teluopyran **80** (88MI1).

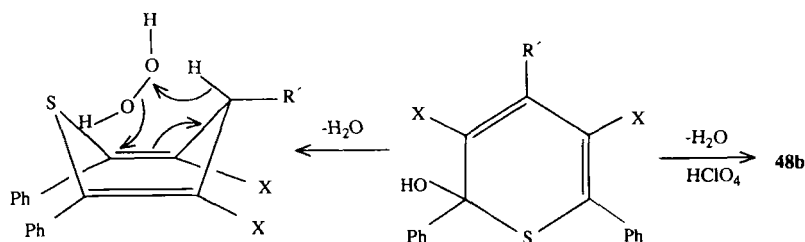
4. Oxygenation of Thiopyrans to Their *S*-Oxides

The *S*-oxygenations of 2*H*-thiopyrans are rare. Sulfone **139a** was obtained from 2*H*-thiopyran **131** ($\text{X} = \text{CH}_2\text{Ac}$) with a H_2O_2 -AcOH mixture (86JPR573). The formation of 2*H*-thiopyran *S,S*-dioxide **139b** analogously obtained from 4*H*-thiopyran **8** ($\text{R} = \text{H}$) was interpreted as arising by a mechanism involving the corresponding thiopyrylium acetate as the catalyst of isomerization (85KGS1042). Similar isomerizations described later (91JOC1674) support the idea.

(139a) $\text{R} = \text{CH}_2\text{Ac}$, $\text{R}' = \text{H}$ (139b) $\text{R} = \text{H}$, $\text{R}' = \text{Me}$ (140a) $\text{R} = \text{Me}$ (140b) $\text{R} = \text{Ph}$ (140c) $\text{R} = \text{H}$ (141a) $\text{R} = \text{R}' = \text{Ph}$ (b) $\text{R} = \text{Ph}$, $\text{R}' = 4\text{-MeC}_6\text{H}_4$ (c) $\text{R} = \text{Ph}$, $\text{R}' = 4\text{-FC}_6\text{H}_4$ (d) $\text{R} = 4\text{-t-BuC}_6\text{H}_4$, $\text{R}' = \text{Ph}$ (e) $\text{R} = 4\text{-FC}_6\text{H}_4$, $\text{R}' = \text{Ph}$ (f) $\text{R} = 4\text{-MeC}_6\text{H}_4$, $\text{R}' = \text{Ph}$ (g) $\text{R} = \text{H}$, $\text{R}' = \text{Ph}$ (142a) $\text{X} = \text{S}$ (142b) $\text{X} = \text{SO}_2$ 

(143)

A number of 4*H*-thiopyrans were converted to their corresponding sulfones with hydrogen peroxide in acetic acid: **132** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$) \rightarrow **140a**, **132** ($\text{R}^1 = \text{R}^3 = \text{Me}$, $\text{R}^2 = \text{Ph}$) \rightarrow **140b** (85KGS1042), **56** ($\text{R} = \text{Ph}$) \rightarrow **141a**, **11** ($\text{Ar}^1 = 4\text{-FC}_6\text{H}_4$, $4\text{-MeC}_6\text{H}_4$, 4-t-



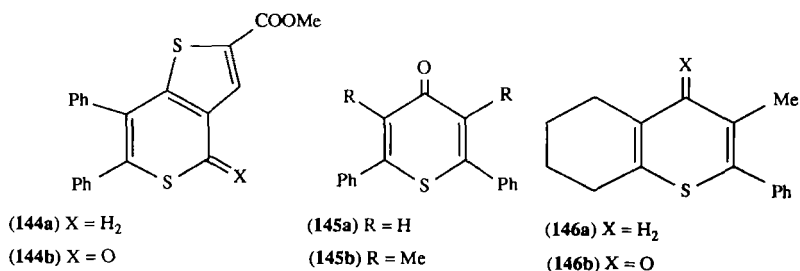
SCHEME 8

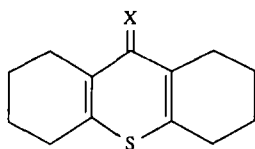
BuC_6H_4 ; $\text{Ar}^2 = \text{Ar}^3 = 4\text{-FC}_6\text{H}_4$, $4\text{-MeC}_6\text{H}_4$) \rightarrow **141b-f** and **142a** \rightarrow **142b** [92JCS(P2)1301, 93CCC869]. It is, however, surprising that 2,4,6-triphenyl-4*H*-thiopyran (**49b**) was only aromatized to **48b** under the same conditions (85KGS1042). One may consider the occurrence of a 4-pseudoaxial hydrogen as being necessary for the aromatization (Scheme 8) in agreement with the finding that additional 3,5-substituents suppress the conformations of 4*H*-thiopyrans with 4-pseudoequatorial phenyl groups (85KGS1042).

4,4-Diphenyl-4*H*-thiopyran (**9**) was oxidized to its *S,S*-dioxide **141g** with RuO_4 (82CJC574). 2,4,4,6-Tetraphenyl-4*H*-thiopyran-*S*-oxide (**143**) was obtained from **56** ($\text{R} = \text{Ph}$) with H_2O_2 -AcOH under mild conditions [92JCS(P2)1301].

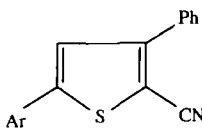
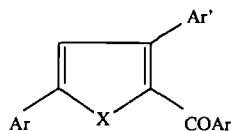
5. Oxygenation of Heteropyrans to Heteropyrones

Some oxidizing agents have been observed to transform the ring methylenes in thiopyran molecules to carbonyl groups. Thus, 2*H*-thiopyran **144a** was found to be air-sensitive, giving 2*H*-thiopyrone **144b** by heating its acetonitrile solution (90SC2749). A series of 4-unsubstituted 4*H*-thiopyrans **49a**, **49** ($\text{R} = \text{Me}$, $\text{R}' = \text{H}$), **146a**, and **147a** was converted into a number of 4*H*-thiopyrones **145a**, **145b**, **146b**, and **147b** in good yields (72–76%) with KMnO_4 in acetone (85KGS1489). Such procedures were also patented (85URP1162804) and extended to analogous selenopyran series (91KGS996).



(147a) X = H₂

(147b) X = O

(148) Ar = Ph, 4-MeOC₆H₄(149) Ar = Ph; Ar' = Ph, 4-MeOC₆H₄; X = S(150) Ar, Ar' = Ph, 4-MeOC₆H₄; X = Se

6. Miscellaneous Oxidations of Thiopyrans and Selenopyrans

Oxidative transformations of 6-aryl-3-cyano-4-phenyl-2*H*-thiopyrans to the corresponding thiophenes **148** have been discussed without experimental details (84CL1973). Similar ring contractions occurred in the oxidation of 2,4,6-triaryl-4*H*-thiopyrans **49** (R = H; R' = Ph, 4-MeOC₆H₄) and analogous 4*H*-selenopyrans **12b** and **12c** with SeO₂ in pyridine in 100°C affording thiophenes **149** or selenophenes **150**, respectively (89KGS767). Appropriate reaction mechanisms are proposed.

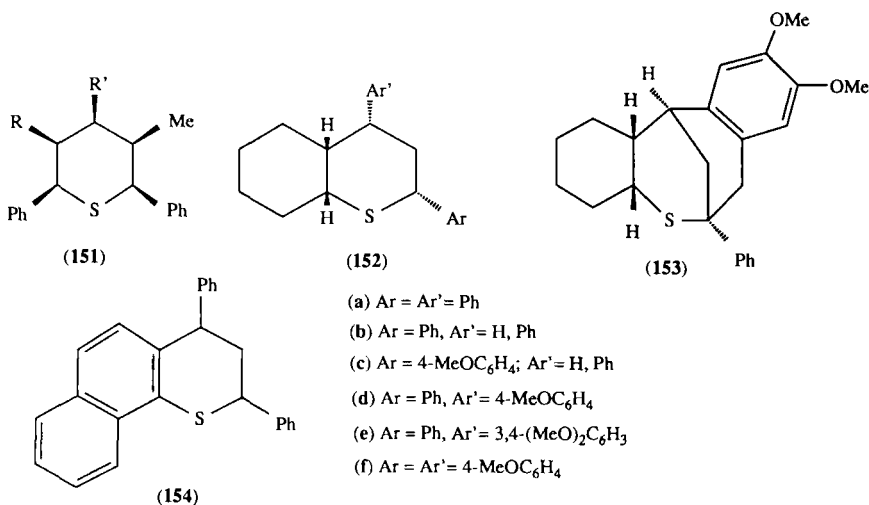
B. DISPROPORTIONATION

A number of examples of the typical thiopyran transformations to corresponding thiopyrylium ions and dihydro or tetrahydro derivatives have been described in the last decade. Similar behavior was found with a selenopyran.

1. Disproportionation of Thiopyrans

The reactions of 4*H*-thiopyrans **132** (R¹, R², R³ = Me, Ph, H; Me, Me, Me; Me, Et, Me; H, Ph, H) with trifluoroacetic acid (TFAA) gave 2:1 mixtures of thiopyrylium salts **133** (X = CF₃CO₂) and all-*cis*-tetrahydrothiopyrans **151** (R = H, Me; R' = Me, Et, H, Ph) except 3,5-dimethyl derivative **132** (R¹ = R³ = Me, R² = Ph), which was unexpectedly stable toward disproportionation (83KGS200; 91KGS181). Annulated 4*H*-thiopyran **134a** (R = 4-MeOC₆H₄) was found to be converted into salts **135a** (R = H, 4-MeOC₆H₄) and a corresponding tetrahydro derivative (91KGS900). The disproportionations of 2*H*-thiopyran **52b** as well as its 4*H*-isomer **50a** proceeded similarly affording in addition to the corresponding thiopyrylium salts the tetrahydro derivative **152a** (81KGS1338, 81KGS1347). The formation of **152b-d** was reached analogously (84KGS898). The same origin of **152e** was, however, accompanied by the intramolecular electrophilic carbocyclization to **153** (86KGS199). Another unexpected but more aromatized by-product **154** had earlier been obtained

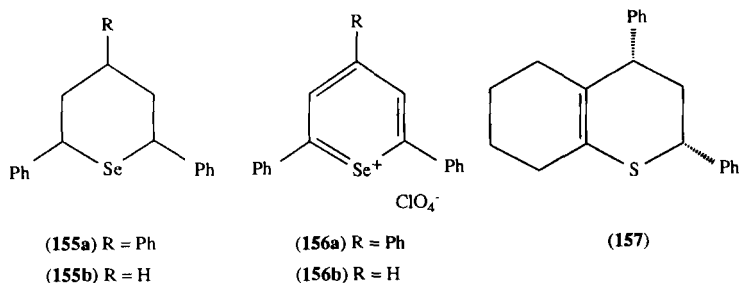
in addition to the disproportionation products from 4*H*-thiopyran **7** (80KGS1337).



Experiments with the deuterium-labeled reagent or the starting compounds **132** ($R^1 = H, R^2 = Ph, R^3 = Me$) has shown that the disproportionations proceed via an initial 3- or 5-protonation of the thiopyran ring followed by a hydride-like transfer to the 2- or 6-position of the reduced thiopyran molecule (81KGS1338, 81KGS1347; 83KGS200). The stereochemistry of the process and the effects of substituents and air-oxygen have been discussed (83KGS200, 83MI1; 91KGS181).

2. Disproportionation of Selenopyrans

2,4,6-Triphenyl-4*H*-selenopyran (**12b**) disproportionated into a mixture of tetrahydro derivative **155a** and perchlorate **156a** after initial treatment with TFAA and then with $HClO_4$ (84KGS1634). An attempt to prepare



2,6-diphenyl-4*H*-selenopyran (**12a**) in the presence of TFAA resulted in a mixture of **14d** with the disproportionation products **155b** and **156b** (see Section III,B).

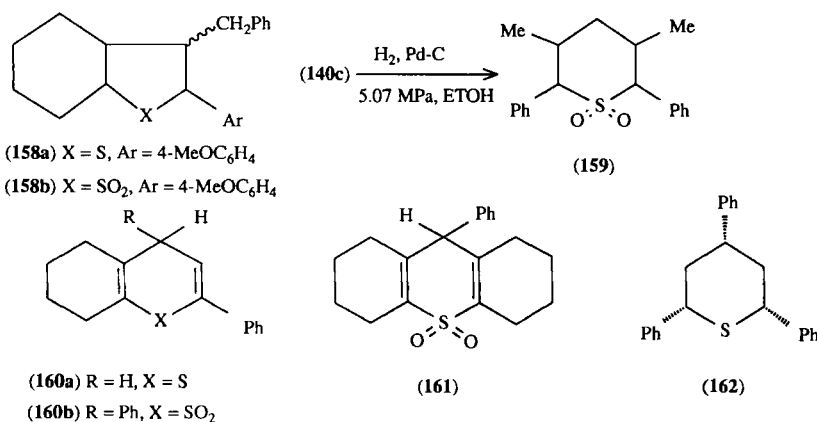
C. HYDROGENATION AND REDUCTION

Further 4*H*-thiopyrans as well as 2*H*-analogs were reduced mainly to their corresponding tetrahydro derivatives. In addition, the hydrogenation of 4*H*-thiopyran-*S,S*-dioxides have been described.

1. Hydrogenation of Thiopyrans

A number of examples using 10% Pd-C catalyst at enhanced pressure and temperature have been reported. Whereas the partial hydrogenation of 4*H*-thiopyran **50a** to its 2,3-dihydro derivative **157** was achieved by a shortening of the reaction time (87KGS614), in other cases only the corresponding tetrahydro products were obtained after complete hydrogen consumption. Thus, the following hydrogenations of 2*H*-thiopyrans were accomplished: **52** ($R' = 3,4-(\text{MeO})_2\text{C}_6\text{H}_3$; $R = \text{Ph}$) \rightarrow **152e**, **52b** \rightarrow **152a**, **52c** \rightarrow **152f**, and **52d** \rightarrow **152d** (81KGS1347; 87KGS614). 4*H*-Thiopyrans **132** ($R^1, R^2, R^3 = \text{Me, Ph, Me; Me, H, Me; Me, Ph, H; Ph, Me, Me; Me, Me, Me; Et, Me, Me; H, Me, Me; Ph, H, Me}$) were hydrogenated to the corresponding all-*cis*-tetrahydro derivatives **151** (87KGS910; 91KGS181). The hydrogenation of **50a,b** and **160a** proceeded analogously (87KGS614).

A ring isomerization giving the by-product **158a** trapped as its *S,S*-dioxide **158b** was observed to compete with processes **506** \rightarrow **152c** ($\text{Ar}' = \text{Ph}$, 87KGS614).



4*H*-Thiopyran-*S,S*-dioxide **140c** underwent hydrogenation to its tetrahydro derivative **159** under the same conditions as the annulated substrates **160b** and **161** (83KGS1058).

2. Reduction of Thiopyrans

The reductions with triethylsilyl hydride (Et_3SiH , TESH) in the presence of TFAA were found to lead to almost the same results as the mentioned catalytic hydrogenation. Thus, 2*H*-thiopyran **52b** was converted to **152a** (81KGS1347) and analogous reductions of 4*H*-thiopyrans were also performed (83KGS200, 83MI2; 87KGS614): **132** ($\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{Ph}$) \rightarrow **162**, **50a** \rightarrow **152a** and **132** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Me}$) \rightarrow **151** ($\text{R} = \text{H}$, $\text{R}' = \text{Ph}$). The reductions proceed via a 3,5-protonation of the 4*H*-thiopyran ring as follows from experiments with **132** ($\text{R}^1, \text{R}^2, \text{R}^3 = \text{H, Ph, H; Me, Ph, H}$) using the deuterium-labeled TESH or TFAA (83KGS200, 83MI2). In some cases HClO_4 instead of TFAA could be used (83KGS200).

D. ISOMERIZATION

The following types of thiopyran isomerizations have been reported in the last decade: valence-bond tautomerism, endocyclic hydrogen shifts and migration of nonhydrogen substituents. Thermal processes will be mentioned here and photochemically induced isomerizations will be discussed in Section V.I.

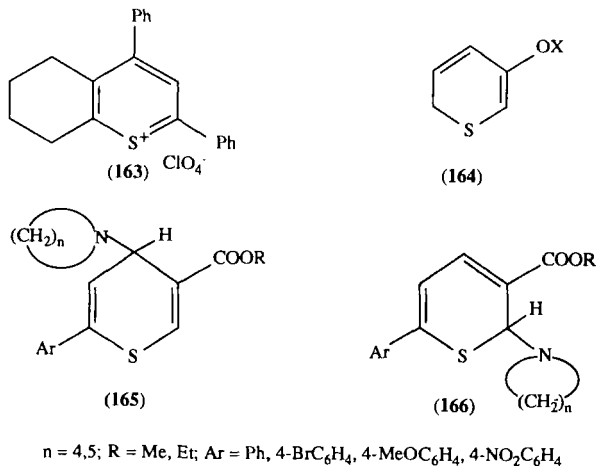
1. Valence-Bond Tautomerism

Sporadic reports of the 2*H*-thiopyran transformation are still available. The electrocyclic ring-opening of 2-benzyl-2,4,6-triphenyl-2*H*-thiopyran (**131**, $\text{X} = \text{PhCH}_2$) was detected by laser flash spectroscopy (86MI1). 2-Amino-2*H*-thiopyran was predicted to be more stable than its valence-bond isomer on the basis of semiempirical MINDO/3 and MNDO calculations (84JPR955).

2. Endocyclic Hydrogen Shifts

Equilibrating mixtures of 2*H*-thiopyrans **107** and their 6*H*-isomers **164** in ratios 4 : 1 ($\text{X} = \text{Si}(\text{i-Pr})_3$) and 1 : 3 ($\text{X} = \text{PO}(\text{OEt})_2$) were found to be formed by heating the partners in inert solvents (91CJC1487).

Thermal isomerizations **50a** \rightarrow **52b** in CD_3CN (81KGS1342) and **55b** \rightarrow **54b** ($\text{R} = \text{R}' = \text{Ph}$) in DMF (81JHC1517) were recognized to be catalyzed by the corresponding thiopyrylium salts **163** and **53b**. Their bimolecular mechanism involves a hydride-like transfer from the $4H$ -thiopyran molecule to position 2 of the salt giving one $2H$ -thiopyran molecule and one molecule of the catalyst. The rate was found to be first-order in **55b** and zero-order in **53b** with the rate constant $k_1 = 2.85 \times 10^7 \exp(-15800 \pm 110/\text{RT})$ for DMF solutions (81JHC1517). The results of a more extended study on equilibria between **55a-f** and **54a-f** in CD_3CN (91JOC1674) are summarized in Table II, Section IV, A. The K_{eq} values exhibit certain similarities with the $2H : 4H$ ratios observed in the borohydride reductions of **53a-f**. Relative rate constants and calculated Gibbs energy differences are discussed with respect to the substituent effects of phenyl and *t*-butyl groups in the studied compounds (91JOC1674). The ΔG values for the isomerization of unsubstituted thiopyrans (**2** \rightarrow **1**) or their 2,4,6-triphenyl derivatives (**55b** \rightarrow **54b**) were estimated to be the same, e.g., -2.3 kcal/mol (86JOC4385).



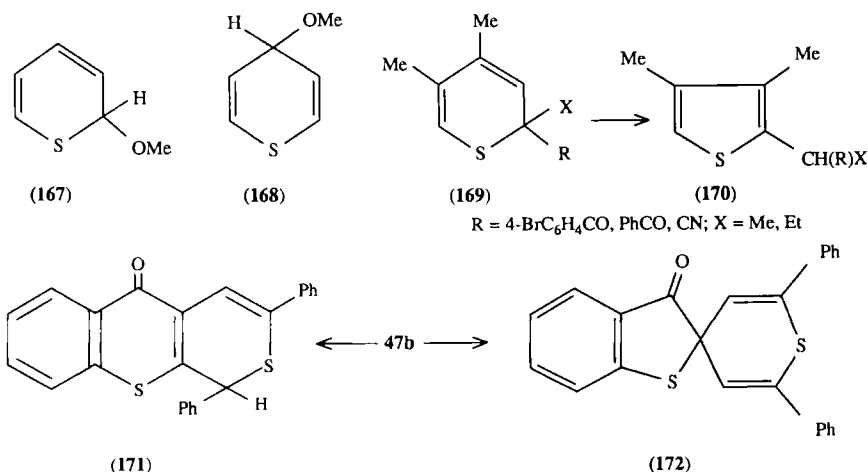
3. Migrations of Nonhydrogen Substituents

Methoxy, alkylamino, and dialkylamino groups bonded to sp^3 heterocyclic carbons are easily migrating substituents that cause a destabilization of the corresponding $2H$ - and $4H$ -thiopyrans. Therefore the $4H$ to $2H$ isomerizations have rarely been accomplished preparatively as in the case of **165** and **166** (81T3693; 82T1705) and where the possibility of any hydrogen migration was excluded with 2-deuterium-labeled substrates (81T3693). In most cases only thermodynamic and/or kinetic investiga-

tions were performed. Thus, the ΔG values -2.3 and -2.5 kcal/mol were obtained for the migration of the methoxy group between unsubstituted methoxythiopyrans (**168** \rightarrow **167**) as well as for their 2,4,6-triphenyl derivatives, e.g., **62** \rightarrow **63** (86JOC4385), showing the general thermodynamic preference of the *2H*-isomers.

The thermal migration of a methoxy group between pairs of a number of various 2,4,6-trisubstituted thiopyrans has been monitored spectroscopically [82JOC960; 86JA3409, 86JCS(P2)271; 87JCS(P2)1427; 89JCS(P2)-1393] and the probable nature of transition states and/or initial states [86JA3409; 87JCS(P2)1427; 89JCS(P2)1393] and substituent effects (86JA3409) have been discussed.

Thermodynamic and kinetic investigations on the migration of variously mono- and disubstituted amino groups were also carried out with the 2,4-di- and 2,4,6-trisubstituted thiopyrans. The rate-determining steps have been found to be the formation of protonated thiopyrans or a proton transfer to the corresponding amine, depending on migrating group character. The isomerizations were proved to proceed via appropriate thiopyrylium salts, for example, **66** \rightarrow **61** + BuNH₂ \rightarrow **65** (R = R' = Ph), e.g., to the thermodynamically more stable *2H*-isomers (82JOC3496; 84JA7082, 84JOC1806; 89G205).



4. Miscellaneous

2H-Thiopyrans **169** have been reported to isomerize to thiophenes **170** on heating in ethanol (90TL115). The sulfoxide **47b** was found to afford *2H*-thiopyran isomer **171** on heating in AcOH but another *4H*-thiopyran,

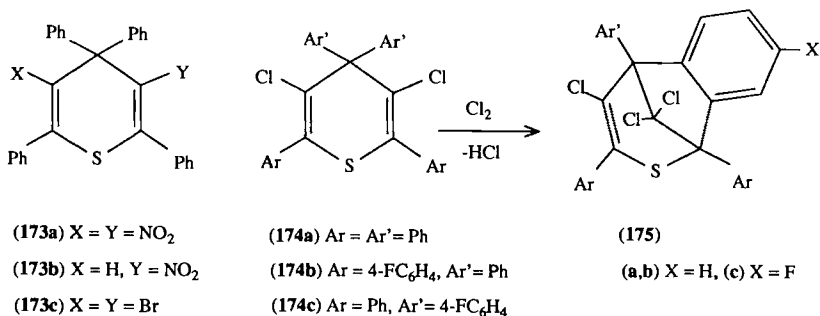
isomer **172** on treatment with a $\text{Cu}(\text{Ac})_2\text{-H}_2\text{O-CH}_2\text{Cl}_2$ mixture at room temperature (84JOC5143).

E. SUBSTITUTION REACTIONS

Further examples of electrophilic substitutions of thiopyrans at position 3 and 5 or at position 4 after deprotonation (83AHC145, Section V.G.) have been described in the last decade. Other substitution reactions are still rare.

1. Simple Electrophilic Substitutions of 4*H*-Thiopyrans

Some 2,4,4,6-tetraaryl-4*H*-thiopyrans **11** were found to undergo easily electrophilic substitution. Thus, the tetraphenyl compound **11** ($\text{Ar}^1 = \text{Ar}^2 = \text{Ar}^3 = \text{Ph}$) was converted to 3,5-dinitroderivative **173a** or to a mixture of **173a** and 3-nitro product **173b** with $\text{HNO}_3\text{-CHCl}_3$ at 0°C . Bromination with $\text{Br}_2\text{-CS}_2$ at 20°C afforded only 3,5-dibromo derivative **173c** (92CCC546). The 3,5-chlorinations of **11** ($\text{Ar}^1 = \text{Ph}$, $4\text{-FC}_6\text{H}_4$, $\text{Ar}^2 = \text{Ar}^3 = \text{Ph}$, $4\text{-FC}_6\text{H}_4$) have been reported to proceed rapidly even at 0°C to **174a-c** being followed by slower transformations to carbocyclized products **175a-c** (92MI2, 92UPI).



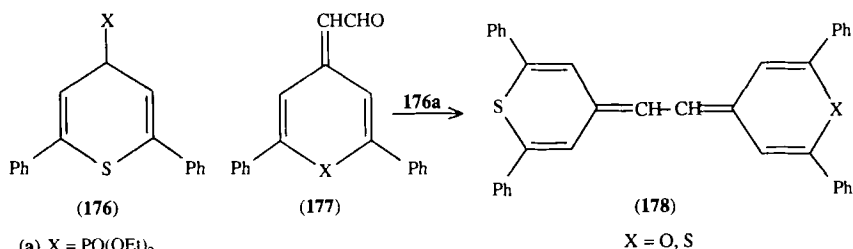
2. Electrophilic Substitutions via Deprotonated Thiopyrans and Selenopyrans

Two examples involving as key intermediates the corresponding thio- or selenopyran anions are mentioned in Section IV, A, 2, e.g., **48e** \rightarrow **60** + **56** ($\text{R} = t\text{-Bu}$) and **54d** + **55d** \rightarrow **59** (85CL1119; 90ACS524). A deuteriodeprotonation of 2,6-diphenyl-2*H*-thiopyran (**87**) to 4-deuterio-2,6-diphenyl-4*H*-thiopyran (**51**) took place after the initial reaction with BuLi-THF at

-77°C followed by decomposition of the reaction mixture with MeOD (82JOC680).

The Wittig–Horner reagent **176a** gave with (thio)pyranylidene aldehydes **177** bis-(thio)pyranylidene products **178** (81JOC184). A deprotonated species formed by the reaction of **87** with BuLi afforded 4-trimethylsilyl derivative **179a**, which could be transformed to a potassium salt of **176b** with a *t*-BuOK–BuLi mixture. The latter was converted to various products with several electrophiles, e.g., **179b** with $\text{CF}_3\text{CO}_2\text{D}$, **179c** with MeI, **181a–c** with (thio)pyranylidene aldehydes **177** or a similar ketone, **182** with corresponding thioxanthone, and **180** with 4-dimethylaminobenzaldehyde (82JOC680).

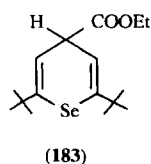
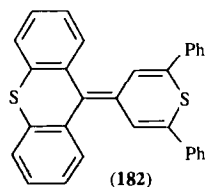
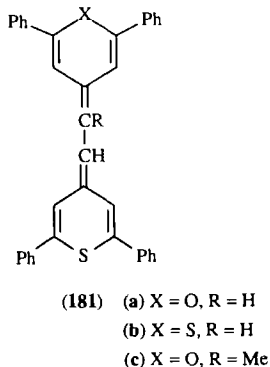
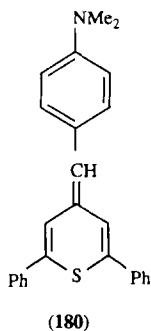
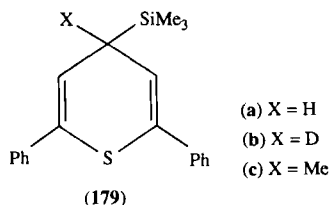
An analogous procedure was realized in the selenium series: 4*H*-selenopyran **136** ($\text{R} = \text{H}$) was converted with LDA at -77°C to a lithium intermediate ($\text{R} = \text{Li}$), which gave ethyl ester **183** by successive treatments with CO_2 and MeCHN_2 (90AG450).



(a) $\text{X} = \text{PO}(\text{OEt})_2$

(b) $\text{X} = \text{SiMe}_3$

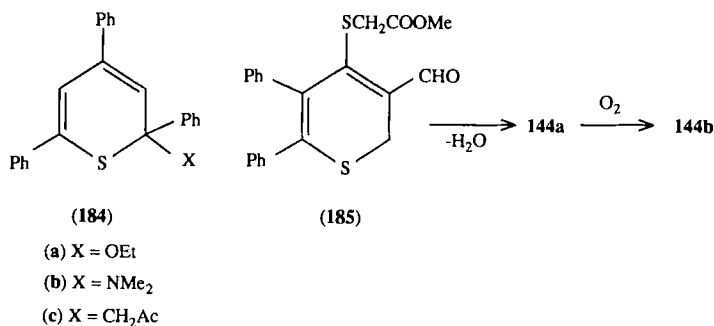
(c) $\text{X} = \text{H}$



3. Nucleophilic Substitution of Thiopyran Derivatives

2-Methoxy-2,4,6-triphenyl-2*H*-thiopyran (**63a**) was converted to the appropriate 2-ethoxy derivative **184a** in boiling EtOH (86JPR373). Similarly, 2-dimethylamino derivative **184b** gave **63a** on heating in MeOH (83ZC333; 86JPR567) or **184c** in a AcMe–AcOH mixture (86JPR573).

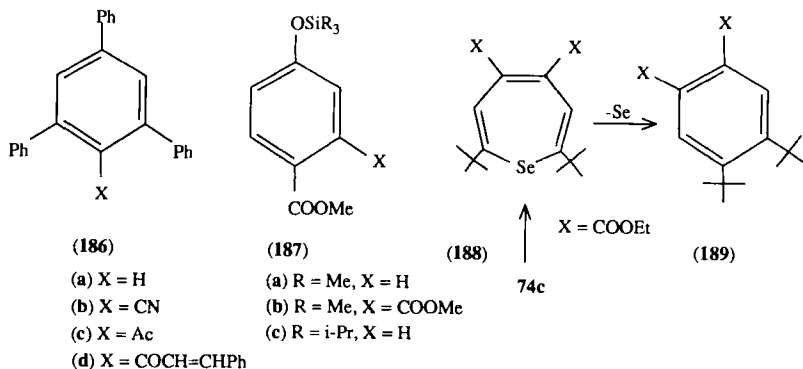
Nucleophilic 4-substitution of 4-chloro-5,6-diphenyl-2*H*-thiopyran-3-carboxaldehyde (**112b**) with a HSCH₂CO₂Et–K₂CO₃ reagent in CH₃CN gave the unstable intermediate **185**, which underwent cyclocondensation to a mixture of **144a** and **144b** (90SC2749).



F. CONVERSION TO OTHER CYCLIC SYSTEMS

1. Intramolecular Cyclizations via Valence-Bond Tautomerism of 2*H*-Thiopyrans

2-Substituted 2,4,6-triphenyl-2*H*-pyrans were found to be easily converted to 1,3,5-triphenylbenzene derivatives. Thus, the hydrocarbon **186a** itself was obtained by heating **184** (X = MeO) in a mixture MeNO₂–Et₃N or **184b** in MeNO₂ only. The same procedures using NCCH₂CO₂Et led



to nitrile **186b** (83ZC333; 86JPR373, 86JPR567). The use of 2-acetyl derivative **184c** as the starting 2*H*-thiopyran yielded **186a** (16%) and **186b** (52%) by treatment with MeONa–MeOH but different yields (52 and 23%) with a NaOH–EtOH–H₂O mixture. On the other hand, only chalcone **186d** was obtained from **184c** by heating with a PhCHO–MeONa–MeOH reagent (86JPR573). Methyl ester **187a** and dimethyl diester **187b** have been reported among other products after the reaction of 2*H*-thiopyran **108a** with MAC (methyl acetylenecarboxylate) or DMAD, respectively (90TL845).

2. Catalytic Decompositions of 4*H*-Selenopyrans

The transformation of diazoester **74c** to benzoic diester **189**, catalyzed with Pd(C₃H₅)₂Cl₂, proceeded as a spontaneous selenium extrusion from unstable seleniepine **188** (90AG450).

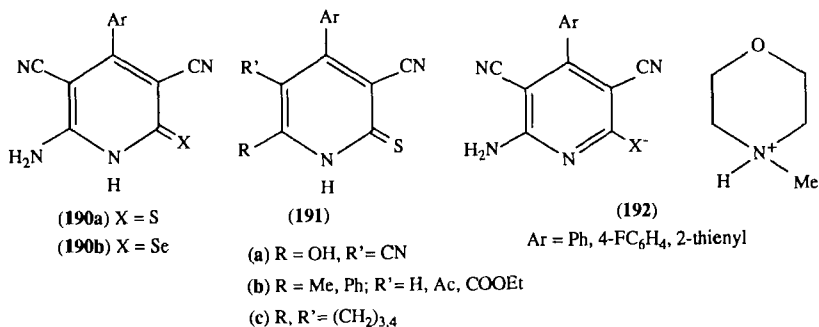
3. Conversion of 4*H*-Thiopyrans and 4*H*-Selenopyrans to Thiopyridones and Selenopyridones

2,6-Diamino-3,5-dicyano-4*H*-thiopyrans (**21**) and analogous 4*H*-selenopyrans **28** were found to be generally transformable to corresponding 6-amino- or 6-hydroxy-2*H*-heteropyrones **190a**, **190b**, or **191a** by initial heating with alcoholic solutions of bases as piperidine (PP), Et₃N, or N-methylmorpholine (MM) and by decomposition of the resulted reaction mixture with protic acids. The hitherto described examples are summarized in Table III. In some cases the salts **192** were trapped [88UKZ615;

TABLE III
2-HETEROPYRONES **190a** AND **191a** PREPARED FROM 4*H*-HETEROPYRANS **21** AND **28**

Heteropyran	R, Ar	Product	X	Reagent	Reference
21	H	190a	S	Et ₃ N	91JCR(S)116
21	Ph	190a ^a	S	MM	89ZOR1323
21	Ph	190a	S	PP	89ZOR622
21	Ph	191a	S	Et ₃ N	86ZN(B)781
28	Ph	190b ^a	Se	MM	89ZOB(L)881 90UKZ287
21	4-ClC ₆ H ₄	191a	S	Et ₃ N	86ZN(B)781
21	4-FC ₆ H ₄	190a ^a	S	MM	89ZOR1323
21	4-MeC ₆ H ₄	191a	S	Et ₃ N	86ZN(B)781
21	2-Furyl	190a	S	PP	89ZOR622
21	2-Thienyl	190a ^a	S	MM	911ZV1643
28	3-Pyridyl	190a ^a	Se	MM	87ZOB(L)1662 88UKZ615

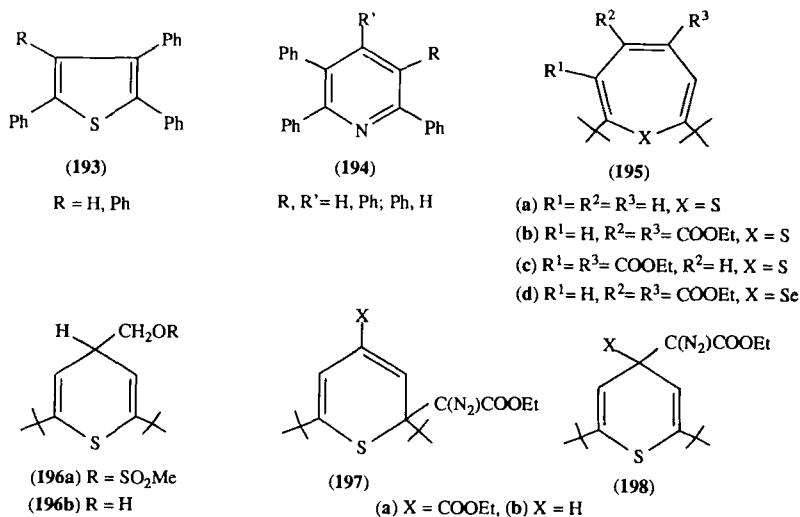
^a Via intermediates **192**.



89ZOB(L)881, 89ZOR1323; 90UKZ2287; 91IZV1643]. Possible mechanisms involving a dehydrogenation step are discussed in detail (86H2023; 87H205; 88UKZ615; 89ZOR622).

4. Ring Contraction of Thiopyrans and Selenopyrans

Thermal isomerization of 2*H*-thiopyrans **169** to thiophenes **170** (90TL115) was mentioned in Section V,D,4. Analogous transformation of **124** to **125** was also reported [88JCS(P1)803]. The similar oxidative ring contraction giving thiophenes **148** was also discussed (Section V,A,6) as well as the SeO₂ oxidation of 4*H*-thiopyrans **132** (R¹ = R³ = H; R² = Ph, 4-MeOC₆H₄) and 4*H*-selenopyrans **12b** and **12c** to ketones **149** and **150** (89KGS767, Section V,A,6).



An early known thermolysis of azido-2*H*-thiopyrans **68** to thiophenes **193** and pyridines **194** (83AHC145, Section V.I.2) was repeated by the same research group (84T3559).

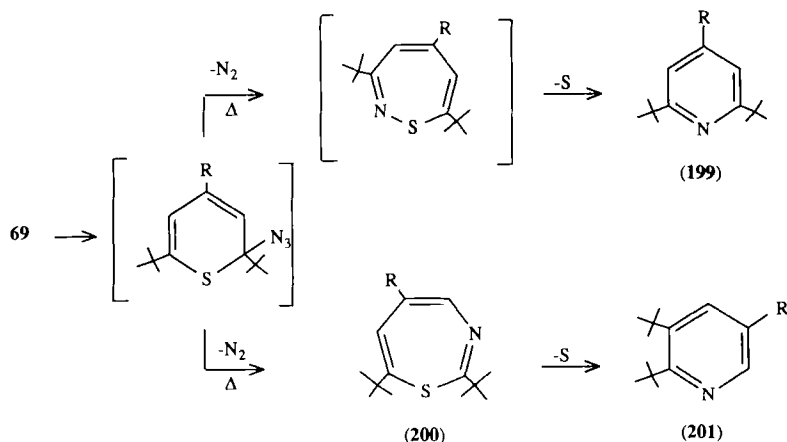
5. Ring Expansion in Thiopyrans and Selenopyrans

This type of transformation usually proceeds via labile carbene or nitrene intermediates thermally generated from the starting heteropyrans. Thus, 2,7-di-(*t*-butyl)thiepine **195a** was prepared from 4*H*-thiopyran **196a** in 29% yield by heating with a AcONa–Ac₂O–AcOH reagent (82TL3195). A nonseparated mixture of isomeric diazothiopyrans **197a** and **198a** was catalytically decomposed into thiepines **195b** and **195c** with Pd(C₃H₅)₃Cl₂ in CHCl₃ at room temperature (85CL1119). Analogous reaction with the selenium analogs, e.g., **74c** → **188**, occurred even at –20°C (90AG450).

The thermolysis of azido-4*H*-thiopyrans **69** (R = H, Ph, *t*-Bu) has been considered to proceed according to Scheme 9, giving mixtures of thiazepines **200** and pyridines **199** and **201** in different ratios depending on reaction conditions [89PS(43)243].

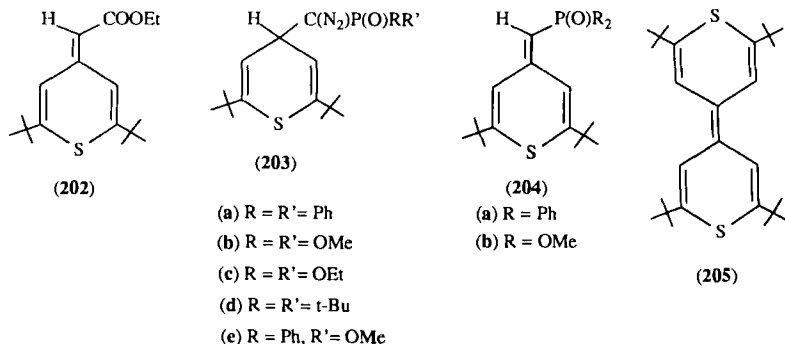
6. Pyranylidene Derivatives from Thiopyrans

Catalytic decomposition of diazocarboxylic ester **198b** with an allyl-coordinated PdCl₂ yielded almost quantitatively thiopyranylidene ester **202** (82CL1843). Analogous phosphorus derivatives **204a** and **204b** were



SCHEME 9

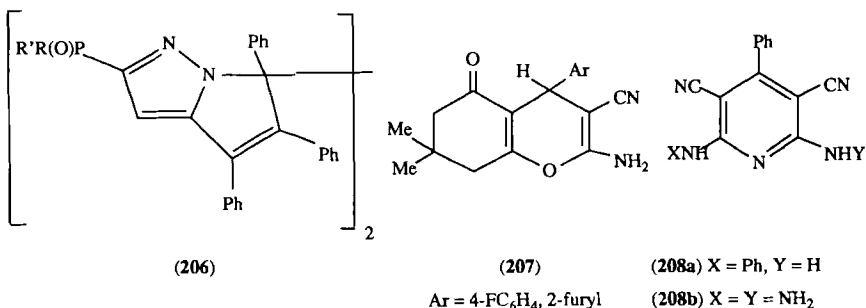
obtained in the same way from diazo-4*H*-thiopyrans **203a** and **203b**, which are accessible in a manner similar to that for **203c–e**, by the reaction of tetrafluoroborate **53d** with the nucleophilic reagents N_2 $CHP(O)RR'-Et_3N$ at $-78^\circ C$. In all cases, bis-thiopyranylidene derivative **205** was formed as a by-product (85T811).

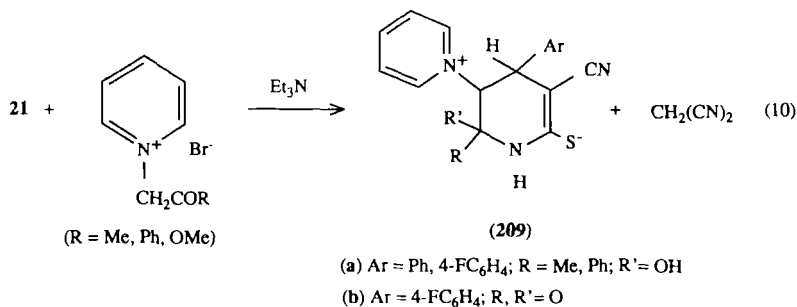


7. Miscellaneous

Dimeric heterocyclic compounds **206** ($R, R' = Ph, Ph; Ph, MeO; MeO; MeO$) were prepared by treatment of diazo-4*H*-thiopyrans **203a**, **203b**, and **203e** with 2,4,6-triphenylthiopyrylium salt **48e** in an $Et_3N-CHCl_3$ solution at $20^\circ C$. A mechanism is discussed in detail (85T811).

The heterocycle in 2,6-diamino-3,5-dicyano-4*H*-thiopyrans **21** could be cleaved with *N*-acetylpyridinium bromides to mesoionic products **209a** and **209b** according to Eq. (10) by treatment with Et_3N in MeOH or EtOH (91ZOR1349). Another general conversion of **21** ($Ar = Ph, 4-FC_6H_4, 2-furyl, 3-$ and $4-pyridyl$) to thiopyridones **191b** and **191c** was achieved with keto derivatives $RCOCH_2R'$ (89ZOR1331). Similar reaction of **21** ($R' = 4-FC_6H_4, 2-furyl$) with dimedone led to 4*H*-thiopyrans **207** and $NCCH_2CSNH_2$ (89ZOR1331). On the other hand, the reactions of **21**



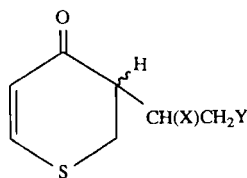


(R = Ph) with PhNH₂ or NH₂NH₂·H₂O at enhanced temperature gave 3,5-dicyanopyridines **208a** and **208b**, respectively (88JPR817).

G. ADDITION REACTIONS

1. Simple Additions

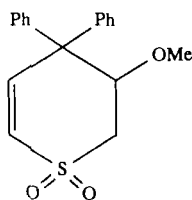
4-Trimethylsilyloxy-2*H*-thiopyran (**108a**) was found to react with methyl-(*E*)-3-nitroacrylate affording 2,3-dihydro-4*H*-thiopyrone **210a**. The similar compound **210b** was obtained among cycloadducts after reaction with CH₂=CHAc (83YZ1096). 4,4-Diphenyl-4*H*-thiopyran-*S,S*-dioxide (**141g**) gave 2,3-adduct **211** on treatment with a KOH–MeOH mixture at enhanced temperature (82CJC574). The addition of H₂Se was observed in the transformation of **12b** → **14e** + **155a** + **156a** in a CF₃CO₂H–Et₂O solution under argon (84KGS1634).



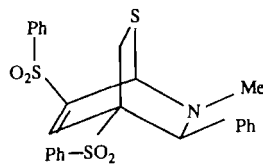
(210)

(a) X = COOMe, Y = NO₂

(b) X = H, Y = Ac



(211)



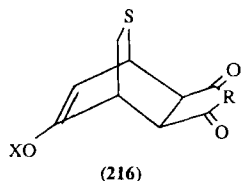
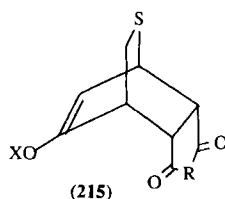
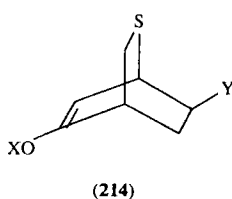
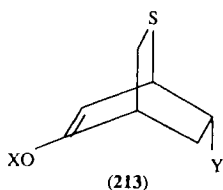
(212)

2. Cycloadditions

a. *Diels–Alder Cycloadditions of Nucleophilic Dienophiles with 2*H*-Thiopyrans.* 3,5-Di-(phenylsulfonyl)-2*H*-thiopyran (**20**) was observed to

be electrophilic enough to add to $\text{PhCH}=\text{NMe}$ affording cycloadduct **212** by heating in toluene at 150°C (91JOC2713).

b. *Diels–Alder Cycloadditions of Electrophilic Dienophiles with 2H-Thiopyrans.* The thermal $[2\pi + 4\pi]$ cycloadditions of methylvinyl ketone, methyl acrylate, acrylonitrile, maleic anhydride (MA), dimethyl maleate (DMM), dimethyl fumarate (DMF), maleimide (MI), and *N*-phenylmaleimide (PMI) to 2*H*-thiopyrans **104a**, **104b**, **106a**, **106b**, **107a**, **107b**, **108a**, **108b**, **108c**, **108e**, and **108f** have been systematically investigated (83YZ1096; 90TL845). The typical cycloadducts may be represented by the series of formulae **213–216**. The endo-isomers **213** and **215** usually predominated over the *exo*-products **214** and **216** (see Table IV). In the cases of DMM and DMF reagents, only the corresponding *trans*-diesters were obtained. Hydrolytic transformations of the enolic molecules corresponding to **213** or **214** to oxo-functionalities were observed in some cycloadditions of **108a** (83YZ1096). Substituent effects on the stereoselectivity are discussed in detail (92CJC2627, 92TL1851) as well as a novel intramolecular version (93TL947). In some cases, 4*H*-thiopyrone and/or its 2,3-dihydro derivative was found as a by-product (91CJC1487).



X, see formulae **108a–b** ;

Y = Ac, COOMe, CN; R = O, NH, NPh

c. *Diels–Alder Cycloadditions of Electrophilic Dienophiles to 4H-Thiopyrans.* The exocyclic double bond in 4*H*-thiopyran **32a** took part in the $[4\pi + 2\pi]$ cycloadditions of $(\text{NC})_2\text{C}=\text{C}(\text{CN})_2$, $\text{EtO}_2\text{CN}=\text{NCO}_2\text{Et}$, MA, and (4-MeO)MIP yielding annulated dihydro thiopyrans **217a** and **218** of probable *exo*-configurations (90BCJ284).

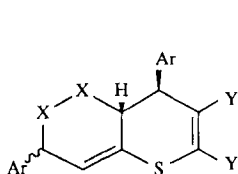
d. $[2\pi + 2\pi]$ Cycloadditions to Thiopyrans. In contrast to the ethylene analogs, acetylenic dienophiles have been reported to afford no Diels–Alder adducts with 2*H*-thiopyrans. Thus, **108b** reacted with MAC

TABLE IV
 STEREOSELECTIVITY IN DIELS-ALDER CYCLOADDITIONS OF 2H-PYRANS^a

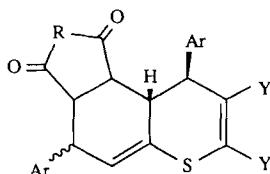
2H-Thiopyran	Ethene	Adducts <i>endo</i> / <i>exo</i>	2H-Thiopyran	Ethene	Adducts <i>endo</i> / <i>exo</i>
104a	PMI	^b	108b	CH ₂ =CHCO ₂ Me	1.7
104b	PMI	4	108b	CH ₂ =CHCN	1
106a	PMI	^b	108c	MA	3
106b	PMI	10	108e	MI	1.2
107a	PMI	^b	108e	PMI	2
107b	PMI	10	108f	MA	6
108a	MI, PMI	10	109	CH ₂ =CHAc	2.5
108b	MA	4	109	MI	3
108b	CH ₂ =CHAc	2.3	109	PMI	2

^a According to Ward *et al.* (91CJC1487).^b *endo*-isomer only.

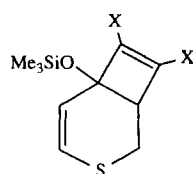
to a complex mixture containing benzoic methyl ester **187c**. Only the $[2\pi + 2\pi]$ cycloadduct **219** and the other benzoic diester **187b** were isolated from a complex mixture after the reaction of more electrophilic DMAD with **108a** (90TL845). On the other hand, 4*H*-thiopyran **32a** possessing the exocyclic C=C bond gave with the same reagent the expected $[4\pi + 2\pi]$ adduct **217b** by heating in benzene under nitrogen (90BCJ284). Recently, the 5,6-cycloadduct from **1** and carbene was reported (93CB485).



(217)



(218)



(219)

(a) X = -C(CN)₂; -N(COOEt)-; Y = COOMe;R = O, 4-MeOC₆H₃N

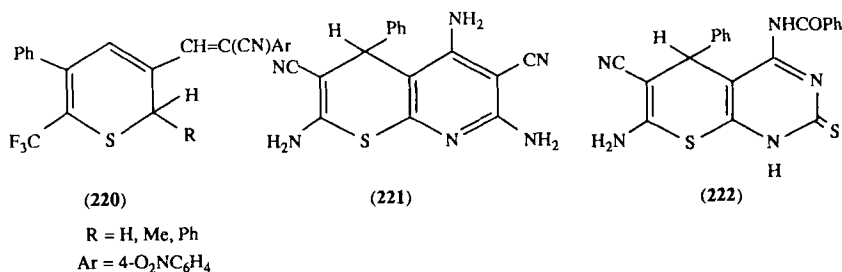
X = COOMe

(b) X = =C(COOMe)-; Y = COOMe

H. FUNCTIONAL GROUP TRANSFORMATIONS

2*H*-Thiopyran-3-carboxaldehydes **17** (R' = H) reacted with 4-nitrobenzyl cyanide to afford the expected condensates **220** (90ZC247). 2,4,6-Triphenyl-2-acetyl-2*H*-thiopyran (**184c**) gave with 2,4-(O₂N)₂C₆H₃NHNH₂, NH₂CONHNH₂, and NH₂CSNHNH₂ corresponding hydrazones (86JPR573). On the other hand, the *ortho* effect between

neighboring amino and cyano groups resulted in the formation of new heterocyclic products **221** and **222** during the cyclocondensations of 2,6-diamino-3,5-dicyano-4-phenyl-4*H*-thiopyran (**21**, R = Ph) with a $\text{CH}_2(\text{CN})_2\text{-Et}_3\text{N}$ reagent at room temperature or by heating with PhCONCS in dioxane, respectively (88JPR817). Several transformations of the carbonyl to appropriate thiocarbonyl groups in 2*H*-thiopyrans with LR were described (88CL1029, 90BCJ2540, 92BCJ2056).

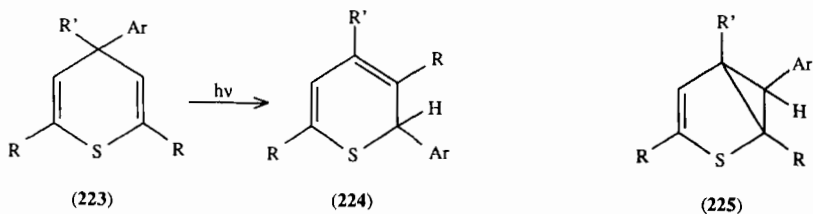


I. PHOTOCHEMICAL REACTIONS

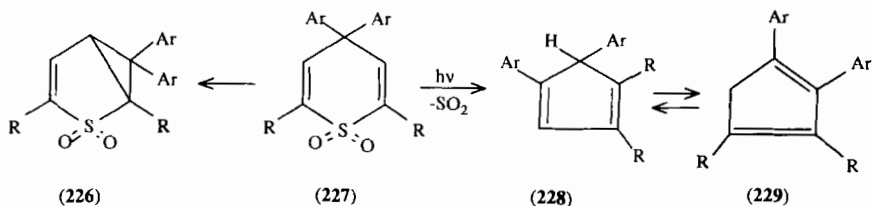
4,4-Disubstituted 4*H*-thiopyrans have been observed to be photochemically transformable into isomeric 2*H*-thiopyrans. The process is accompanied by migration of one 4-aryl group to position 2 as follows from the accomplished conversions: **223a** → **224a** (82CJC574), **223b** → **224b**, and **223c** → **224c** [91JCS(P2)2061; 92JCS(P2)1301], **223d** → **224d**, **223e** → **224e**, and **223f** → **224f** [92JCS(P2)1301, 92UP1]. These photochemical transformations proceeded as di- π -methane rearrangements (**223** → **225** → **224**) as justified by the spectral identifications of **225a** and **225c** [82CJC574; 91JCS(P2)2061] or even the isolation of **225c** [92JCS(P2)1301]. 2,4,4,6-Tetraaryl-4*H*-thiopyrans have been observed as a rule to be photochromic, and alternative structures responsible for the photocoloration have been discussed [91JCS(P2)2061, 91PS(59)545; 92CCC1326, 92JCS(P2)1301].

4,4-Diaryl-4*H*-thiopyran-*S,S*-dioxides were not photochromic; they exhibit the second type of the photochemical di- π -methane rearrangements, e.g., **227a** → **226a** (82CJC574), **227b** → **226b** and **227c** → **226c**. If two aryl groups were at positions 2 and 6, then the major photochemical path involved SO₂ extrusion, e.g., **227b** → **228b** and **227c** → **228c**, followed by thermal isomerization of the photoproducts to **229b** and **229c**. The analogous photolysis of sulfone **142b** gave a mixture of hydrocarbons **230a** and **230b** (93CCC869, 93CCC882).

Photochemical transformations of azido-2*H*-thiopyrans **68** to thiepinines **193** and pyridines **194** were also reported (84T3559).



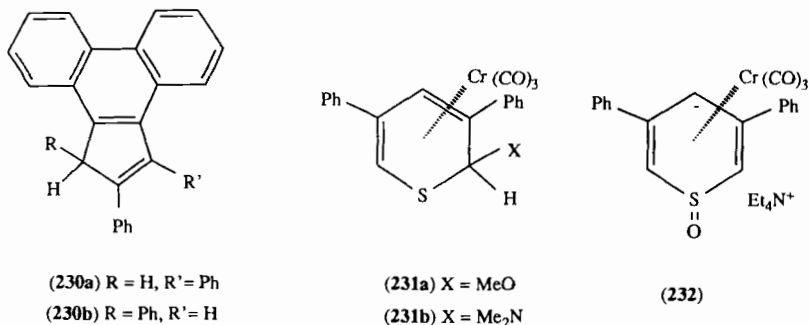
- (a) R = H, Ar = R' = Ph
 (b) R = Ar = Ph, R' = Me
 (c) R = R' = Ar = Ph
 (d) R = 4-MeC₆H₄, R' = Ar = Ph
 (e) R = 4-FC₆H₄, R' = Ph = Ar
 (f) R = Ph, R' = Ar = 4-FC₆H₄



- (a) Ar = Ph; R = H
 (b) Ar = Ph; R = Ph, 4-t-BuC₆H₄, 4-FC₆H₄, 4-MeC₆H₄
 (c) Ar = 4-t-BuC₆H₄, 4-FC₆H₄, 4-MeC₆H₄; R = Ph

J. FORMATION OF METALLIC COMPLEXES

The transformation of 3,5-diphenyl-2*H*-thiopyran (**129**) to tricarbonyl metallic complexes (81AG304; 82CB1775; 83CB514) was mentioned in Section V,A,1. Further tricarbonyl chromium complexes **231a** and **231b** were obtained from the salt **232** with MeOSO₂F or Me₂NSO⁺BF₄⁻, respectively (83CB514).



VI. Physical Properties and Theoretical Chemistry

A. X-RAY CRYSTALLOGRAPHY AND MOLECULAR STRUCTURE

2,6-Diamino-3,5-dicyano-4-phenyl-4*H*-thiopyran **21** ($R = Ph$) and its 4*H*-selenoanalog **28** ($Ar = Ph$) exhibit similar molecular geometries, e.g., (a) boat conformations of the heterocycles and (b) similar bond lengths and angles not directly bound to heteroatoms (Fig. 1). A somewhat surprising asymmetry in the crystal packing is evidently due to the developed system of hydrogen bonds. The unit cells contain two conformers differing in the torsion angles about the pseudoaxial 4-phenyl groups [89ZOB(L)881, 89ZOR1323].

The annulation of 4*H*-thiopyran and cyclohexane rings in **50a** results in the planarity of the heterocycle and a half-chair conformation of the carbocycle (81KGS1342). On the other hand, a boat conformation of the 2*H*-thiopyran ring was found in the crystal of **224b** [91JCS(P2)2061]. Other geometrical parameters were within the limits of the expected values (Fig. 2).

Crystal and molecular structures of 2,4,4,6-tetraphenyl-4*H*-thiopyran-1-oxide (**143**) and the corresponding 1,1-dioxide **141a** were investigated to show the boat conformations of the heterocycles as well as an interesting

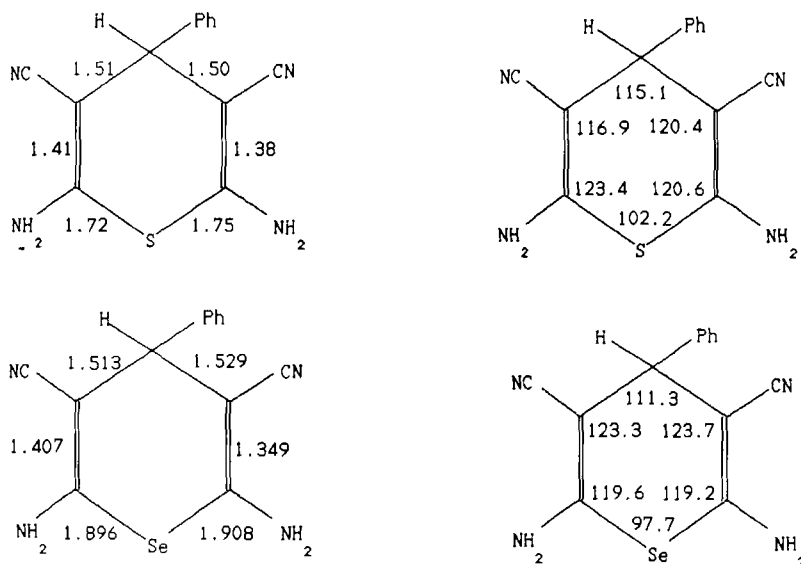


FIG. 1. Bond lengths and angles for 4*H*-thiopyran **21** ($R = Ph$) and 4*H*-selenopyran **28**.

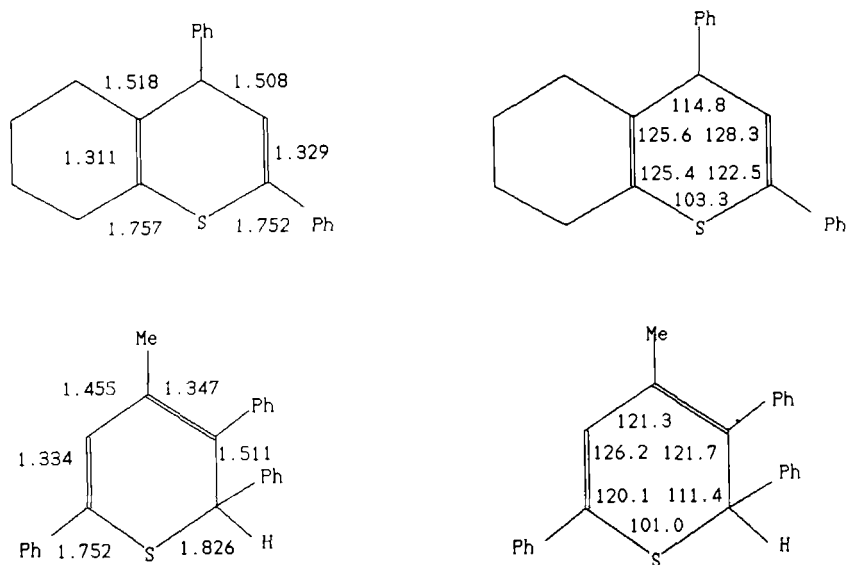


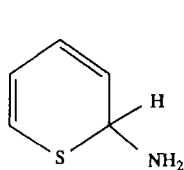
FIG. 2. Bond lengths and angles for *2H*-thiopyran **224b** and *4H*-thiopyran **50a**.

complexation with benzene [92AX(C)1495, 92AX(C)1497]. Typical structural features of the corresponding *4H*-thiopyran **56** ($R = \text{Ph}$), its *S*-oxide **143**, and *S,S*-dioxide **141a** appear to be the values of C—S—C , C—SO—C , and $\text{C—SO}_2\text{—C}$ angles (101.3 , 99.8 , and 105.2°) as well as significant deviations of the phenyl groups from the double-bond planes.

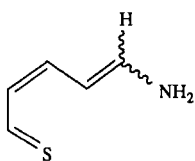
B. MOLECULAR ENERGY AND ELECTRONIC STRUCTURE

MO calculations were performed rarely for thiopyrans except for an MNDO study of **2** [84ZN(A)267]. Charge distribution and orbital interaction concepts were explored in an interpretation of model reactions of thiopyrylium ions with azides giving **68** and the corresponding 3,5-unsubstituted thiopyrans (84T3549) as well as for the equilibria between **1** and **2** or **167** and **168**, respectively (92JOC4431).

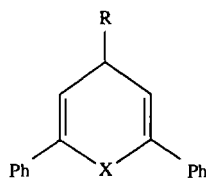
Valence-bond isomerization of model 2-amino-*2H*-thiopyran (**233**) and acyclic isomer **234** was investigated by the semiempirical MINDO/3 and MNDO methods (82KGS1028; 84JPR955). Although the results qualitatively agree with experimental findings, similar applications have to be taken with care because of the inability of NDO-like methods to describe the molecular geometry of conjugated systems.



(233)



(234)



(235a) R = Ph, X = S

(235b) R = H, X = S

(235c) R = H, X = Se

C. NUCLEAR MAGNETIC RESONANCE

Interpretation of ^1H and ^{13}C NMR spectra has been a part of almost all synthetic work on heteropyrans. Complete assignments using 2D NMR or other more advanced techniques still seem to be exceptional [92JCS(P2)1301]. Typical values of ^1H and ^{13}C NMR characteristics for some *2H*- and *4H*-heteropyrans are given in Tables V, VI, VII, and VIII.

^1H NMR spectroscopy frequently has been used in kinetic studies, for example, in the isomerization of 2,4,6-triphenyl-*4H*-thiopyran **56** (R = Ph) to its *2H*-isomer **60** (R = H, 81JHC1517). ^{125}Te NMR spectra were also measured for *4H*-teluopyran **77** and related compounds (88MI1). Oxo-enol tautomerism of 4-hydroxy-*2H*-thiopyrans **110a-c** in the solid state as well as in CDCl_3 solution was successfully studied by ^{13}C NMR [86JCS(P2)1887].

D. ELECTRONIC SPECTRA

Ultraviolet spectra of heteropyrans have been used mainly for characterization purposes. No theoretical calculations of the spectral patterns have yet been done. Typical UV absorption characteristics of some thiopyrans and teluopyrans are collected in Table IX. Analogous insight into the UV absorption of selenopyrans is still lacking.

Ultraviolet spectrophotometry was used to follow the course of the photoreduction of thiopyrylium salts to their corresponding *4H*-thiopyranyl radicals (85BCJ2600) as well as the kinetics of thiopyrylium salt transformations to thiopyrans with various nucleophiles (84JA7082, 84JOC1806; 86JA3409).

Ultraviolet absorption spectra were also applied in the investigations on photophysical, photochemical, and photochromic behavior of some

TABLE V
¹H-NMR DATA FOR SOME HETERO-2*H*-PYRANS

Compound	Chemical shifts ^a of substituent at position					Reference
	2	3	4	5	6	
2,6-Diphenyl-2 <i>H</i> -thiopyran	4.7 dd (5.7, 1.2)	5.66 dd (5.7, 9.3)	6.28 ddd (9.3, 6.0, 1.2)	6.68 d (6.0)	7–7.6 m	82JOC680
2-Diethylamino-4,6-diphenyl-2 <i>H</i> -thiopyran	5.35 (6.7, 0)	5.85 (0.5)	^b	6.15 (0.0, 0.5)	^b	82JOC3496
2,6-Di-tert-butyl-2-methoxy-4-phenyl-2 <i>H</i> -thiopyran	1.10 s	5.48 s	7.40	6.33 s	1.33 s	86JA3409
2,6-Diphenyl-2-methoxy-2 <i>H</i> -thiopyran	7.2–7.7 m	5.47 m (7.7, 0.8)	6.65 m (7.7, 6.0)	6.75 (6.0, 0.8)	7.2–7.7 m	86JCS(P2)271
2,4,6-Triphenyl-2-acetonyl-2 <i>H</i> -thiopyran	7.08–7.65 m	6.38 s	7.08–7.65 m	6.80 s	7.08–7.65 m	86JPR573
2,4,6-Triphenyl-2-dimethylamino-2 <i>H</i> -thiopyran	7.02–7.77 m	5.57 s	7.02–7.77 m	6.59 s	7.02–7.77 m	86JPR567
3-Formyl-6-(4-dimethylaminophenyl)-2 <i>H</i> -thiopyran	3.61 s	9.54 s	6.95 d (7.0)	6.35 d (7.0)	6.62 m	87S456
di-tert.butyl 2 <i>H</i> -thiopyran-2,2-dicarboxylate	1.4	5.81 (1.20, 9.94, 0.53)	6.82 (–0.37, 9.94, 7.04)	6.23 (0.53, 7.04, 9.86)	6.26 (9.86, 1.20, –0.37)	88JCS(P1)803
4-Trimethylsilyloxy-2 <i>H</i> -thiopyran	3.37 d (5.5)	4.68 ddt (0.5, 1.5, 5.5)	0.22 s	5.86 dd (1.5, 10.0)	6.32 dd (0.5, 10.0)	91CJC1487

^a Coupling constants (Hz) are given in parentheses.

^b Not given.

TABLE VI
¹H-NMR DATA FOR SOME HETERO-4*H*-PYRANS

Compound	Chemical shifts ^a of substituent at position					Reference
	2	3	4	5	6	
2,4,6-Triphenyl-4 <i>H</i> -thiopyran	7.3 m	6.0 d	4.5 t	6.0 d	7.3 m	81JHC1517
2,6-Diphenyl-4 <i>H</i> -thiopyran	7.1–7.6 m	5.85 t (4.5)	3.1 t (4.5)	5.85 t (4.5)	7.1–7.6 m	82JOC680
2,6-Di-tert-butyl-4-methoxy-4-phenyl-4 <i>H</i> -thiopyran	1.26 s	5.39 s	7.32	5.39 s	1.26 s	86JA3409
2,6-Diphenyl-4-methoxy-4 <i>H</i> -thiopyran	7.4–7.7	6.23 d (5.2)	5.18 t (5.2)	6.23 d (5.2)	7.4–7.7	86JCS(P2)271
2,6-Di-tert-butyl-4 <i>H</i> -thiopyran	^b	5.62 t (4.7)	2.66 t (4.7)	5.62 t (4.7)	^b	880MI1
2,4,6-Triphenyl-4 <i>H</i> -selenopyran	7.05–7.52 m	6.12 d	4.19 t	6.12 d	7.05–7.52 m	84KGS1634
2,6-Di-tert-butyl-4 <i>H</i> -selenopyran	1.17 s	5.87 t (5.0)	2.58 t (5.0)	5.87 t (5.0)	1.17 s	88MI1
2,6-Di(<i>p</i> -methoxyphenyl)-4-phenyl-4 <i>H</i> -selenopyran	7.20–7.51 m	6.12 d (4.13)	4.24 t (4.21)	6.12 d (4.13)	7.20–7.51 m	89KGS767
4-Ethoxycarbonyl-2,6-di-tert-butyl-4 <i>H</i> -selenopyran	1.16 s	5.96 d (4.0)	3.03 t (4.0)	5.96 d (4.0)	1.16 s	90AG450
2,6-Di-tert-butyl-4 <i>H</i> -telluropyran	1.20 s	6.02 t (5.4)	2.66 t (5.4)	6.02 t (5.4)	1.20 s	88MI1

Note: The assignment of the 3–5 signals may be interchanged.

^a Coupling constants (Hz) are given in parentheses.

^b Not given.

TABLE VII
¹³C-NMR SHIFTS FOR SOME HETERO-2*H*-PYRANS

Position/substituent						Reference
1	2	3	4	5	6	
S	61.1 (CH ₂) ₄ N	114.5 COOEt	134.1 H	114.6 H	145.2 <i>p</i> -MePh	81T3693
S	21.7 H, H	122.5 COMe	132.9 H	124.6 COOMe	145.8 H	85JOC1545
S	87.8 Ph, OMe	115.8 H	^a Ph	114.7 H	^a Ph	86JPR373
S	39.98 Ph, H	147.42 NO ₂	^a H	113.31 H	^a <i>p</i> -MePh	90T1951
S	25.6 H	93.3 H	149.7 Me ₃ OSi	122.7 H	125.8 H	91CJC1487
S	47.76 Ph	141.02 Ph	132.71 Ph	123.10 H	125.02 Ph	92JCS(P2)1301

^a Not given.

TABLE VIII
¹³C-NMR SHIFTS FOR SOME HETERO-4*H*-PYRANS

Position/substituent						Reference
1	2	3	4	5	6	
S	135.0 COOMe	124.7 COOMe	55.1 (CH ₂) ₄ N	114.4 H	134.7 <i>p</i> -MeOPh	81T3693
S	^b Ph	119.5 H	35.7 (Me) ₃ Si, H	119.5 H	^b Ph	82JOC680
S	^b Ph	116.69 H	28.85 H	116.69 H	^b Ph	82JOC680
S	151.1 NH ₂	72.4 CN	43.5 Ph, H	72.4 CN	151.1 NH ₂	85H3107
S	133 COOMe	125.9 COOMe	59.7 H, NMe ₂	125.9 COOMe	133 COOMe	85JOC1545
S	146.6 Ph	135.8 Me	180.5 =O	135.8 Me	146.6 Ph	85KGS1489
S	137.9 H	131.5 H	179.5 =O	131.5 H	137.9 H	86JCS(P2)1887
S	125.1 ^a <i>i</i> -PrS	128.1 ^a H	32.2 H, H	128.3 ^a H	131.8 ^a MeS	88LA933
S	131.27 Ph	123.18 H	53.41 Ph, Ph	123.18 H	131.27 Ph	92JCS(P2)1301
Te	146.2 <i>t</i> -Bu	123.6 H	39.8 H, H	123.6 H	146.2 <i>t</i> -Bu	88MI1

^a The assignment of 3–5 and 2–6 signals may be interchanged.

^b Not given.

TABLE IX
ABSORPTION SPECTRA FOR SOME 2*H*- AND 4*H*-HETEROPYRAN CHROMOPHORES

Substituent at position						λ_{\max}	log ϵ	Reference
1	2	3	4	5	6			
S	COOMe	COOMe	(CH ₂) ₄ N, H	H	Ph	220, 248		81T3693
S	H	H	Ph, Ph	H	H	240, 285	1470, 1090 ^a	82CJC574
S	Ph	Ph	Ph, H	Ph	Ph	230, 260, 325	4.39, 4.13, 3.8	84T3539
S	Ph	Ph	H, H	Ph	Ph	225, 265	4.7, 4.4	84T3539
Te	tert-Bu	H	X ^b , H	H	tert-Bu	440	3130 ^a	88M11
Te	tert-Bu	H	H, H	H	tert-Bu	345, 420	3900, 150 ^a	88M11
S	(CH ₂) ₄ , H	COOEt	H	H	Ph	224, 281, 366		81T3693
S	tert-Bu, OMe	H	Ph	H	tert-Bu	308	4.41	86JA3409
S	Ph, CH ₂ COCH ₃	H	Ph	H	Ph	260, 345	4.38, 3.72	86JPR573
S	Ph, NMe ₂	H	Ph	H	Ph	251, 349	4.34, 3.79	86JPR567

^a Shoulder.

^b X = 2,6-Di-tert-butyl-4*H*-telluropyran-4-yl.

2*H*-thiopyrans (86M11) and in a study of photochemical and thermochemical reductions of tetrafluoroborate **48d** to an appropriate 4*H*-thiopyranlyl dimer (89BCJ2279).

E. INFRARED SPECTRA

Infrared absorption spectra of heteropyrans have been used mainly for the identification of functional groups. Assignments of the bands belonging to heterocyclic bond vibrations (C=C, C—S, C—Se, C—Te) have not been common. As a rule, 4*H*-heteropyrans exhibit maxima at higher wave numbers than 2*H*-isomers. Typical IR absorption maxima for heteropyrans are shown in Table X.

TABLE X
SOME INFRARED SPECTRAL CHARACTERISTICS OF 2*H*- AND 4*H*-HETEROPYRANS

	$\bar{\nu}_{\max}(\text{cm}^{-1})$	Reference
4-(4-Methylphenyl)-2,4,6-triphenyl-4 <i>H</i> -thiopyran	1680, 1640	91JCS(P2)2061
2,6-Diamino-4-phenyl-4 <i>H</i> -thiopyran-3,5-dicarbonitrile	3440, 3400, 3200, 3020, 2180, 1650	86ZN(B)781
6-Isopropylthio-2-methylthio-4 <i>H</i> -thiopyran	2960, 2920, 2860, 1595, 1460, 965, 860	88LA933
4,4-Diphenyl-4 <i>H</i> -thiopyran-1,1-dioxide	1295, 1115	82CJC574
2,6-Diamino-4 <i>H</i> -thiopyran-4-phenyl-4 <i>H</i> -thiopyran	3440, 3400, 3340, 3200, 3020, 2180	86LA1639
3,5-Dimethyl-2,4,6-triphenyl-4 <i>H</i> -thiopyran-1,1-dioxide	1288, 1130, 1600, 1670	85KGS1042
4-Trimethylsilyloxy-2 <i>H</i> -thiopyran	3045, 1627	91CJC1487
Dimethyl 2 <i>H</i> -pyran-2,2-dicarboxylate	3000, 2940, 1730, 1430	88JCS(P1)803
2-Dimethylamino-2,4,6-triphenyl-2 <i>H</i> -thiopyran	1612	86JPR567
3-Cyano-6-phenyl-2 <i>H</i> -thiopyran	2185, 1600, 1520, 1475, 750, 685	80JHC405
sym-Octahydroselenooctacen	1675, 1446	81KGS640
3,5-Dimethyl-2,6-diphenyl-4 <i>H</i> -selenopyran	1635, 1610, 1590	82ZOR2595
2,4,6-Triphenyl-4 <i>H</i> -selenopyran	1650, 1615, 1595	82ZOR2595

F. OTHER SPECTROSCOPIC TECHNIQUES

Mass spectral measurements have usually been used in the verification of molecular formulae of heteropyrans, where the field desorption technique seems to be the most promising (88MI1). A detailed study of fragmentation patterns for polysubstituted 4*H*-thiopyrans **173a–c** and **174a–c** is available (92CCC546). The formation of ionic species M^+ , $(M-I)^+$, and/or $(M-Ar)^+$ and the H_2S extrusion appear to be the main fragmentation paths of 4*H*-thiopyrans (82JOC680; 89ZOR2382; 92CCC546).

Electron spin resonance measurements were successfully used for the identification of various radical species originating from 4*H*-thio- and 4*H*-selenopyran derivatives in the elucidation of reaction mechanisms [85BCL2600; 90ZOB(L)1012]. A hyperfine splitting analysis was used for the clarification of spin delocalization in some more extended π -electron systems containing heteropyranyl fragments [90ZOB(L)1012]. This analysis based on ESR and ENDOR measurements of 4*H*-thiopyranyl radical **235a** was also confirmed by MacLachlan LCAO MO calculations (85BCL2600).

G. MISCELLANEOUS

Nano- and microsecond laser flash spectroscopy was employed to clarify photophysical effects on benzyl group migration in 2*H*-thiopyran **60** ($R = PhCH_2$, 86MI1).

Relative heteroatom effects (O, S, Se) were followed in the polarographic reduction of some pyrylium and heteropyrylium salts to 4*H*-heteropyran-like radicals **235b** and **235c** [86ZOB(L)863]. A voltamperometric study of 4*H*-thiopyrans **49b** and **49** ($R = Me$, $R' = Ph$) on a rotating disk electrode has shown their electrooxidations to be easier in comparison to their oxygen analogs (84KGS318). Cyclic voltammetric measurements were carried out on the transformation of hexafluorophosphate **76** to dimeric 4*H*-teluopyran derivative **80** (88MI1) as well as on some bis-onium dyes containing heteropyranyl (S, Se, Te) fragments (88MI2). Anodic heteroaromatizations accompanied by a CC bond cleavage in thiopyran **134a** ($R = 4-MeOC_6H_4$) and selenopyran **134b** ($R = 2-thienyl$) were investigated (91KGS900). Formation of thiopyranyl and selenopyranyl dimers was considered in the polarography of some 2,4,6-triarylheteropyrylium salts [86ZOB(L)863].

The pK_a values for 3-phenyl- and 6-methyl-3-phenyl-2*H*-thiopyran-*S,S*-dioxides have been discussed in connection with the aromatic stabilization energies of their corresponding anions (91JOC4218).

VII. Miscellaneous Properties

2-Methyl-2*H*-thiopyran was identified among 20 other components in the oil from *Allium sativum* (88MI3). The supplementation of boiler chick feeds with various selenium compounds including 4*H*-selenopyran **13b** has been investigated (90MI1).

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Halogenation of Heterocycles: III. Heterocycles Fused to Other Aromatic or Heteroaromatic Rings

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I. Introduction

Part 1 (93AHC291) discussed halogenation procedures and their application to five-membered heterocycles; Part 2 (93AHC271) covered the monocyclic six- and seven-membered rings. This final part summarizes halogenation of heterocycles fused to one or more benzene rings and condensed systems made up of at least two heteroaromatic rings. Emphasis is mainly on bicyclic systems.

II. Halogenation of Condensed Heterocycles

A. BENZO DERIVATIVES OF FIVE-MEMBERED HETEROCYCLES

A benzene ring fused to a π -excessive heterocycle is less reactive toward electrophiles than the heteroring, and it frequently reduces the reactivity of the latter, and may modify the orientation of substitution. Where the

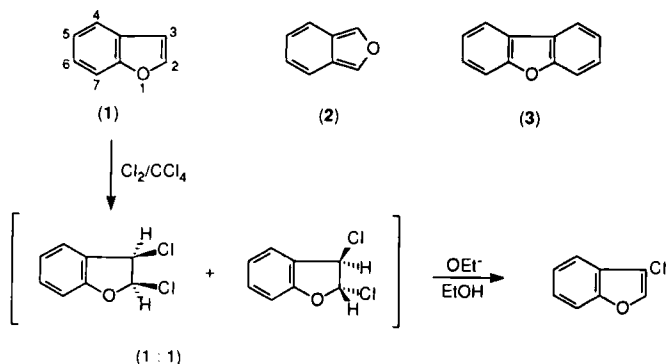
heterocycle has a basic nitrogen atom, acidic halogenating reagents tend to protonate (or complex) that site thereby reducing reactivity toward positive halogen species. Conversely, nucleophilic halogenations usually occur with more facility in the fused benzene ring. Substituents can, of course, modify this general behavior.

1. Benzofurans

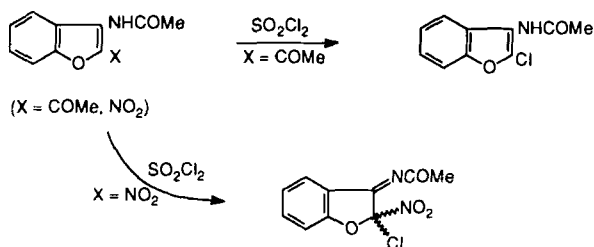
a. *Benzo[b]furans*. Aspects of the halogenation of benzo[*b*]- (1), benzo[*c*]-furan (2) [74HC(29)1; 80AHC(26)135; 84MI18], and dibenzofuran (3) [51MI2; 84AHC(35)2] have been discussed in earlier reviews. Most is known about 1, which tends to be halogenated by an addition–elimination mechanism to give 2- and 3-substituted products [76JCS(P2)266]. The high 2,3-bond order in this compound contributes to the facility of halogen addition.

When 1 was chlorinated in acetic acid or carbon tetrachloride, at 0 or 25°C, respectively, an equimolar mixture of *cis*- and *trans*-2,3-dichloro-2,3-dihydrobenzo[*b*]furans was obtained. Presumably there is little steric hindrance to *cis*-addition. With iodobenzene dichloride the *trans*-isomer predominated. As expected, an ethanolic solution of sodium ethoxide converted both isomers into 3-chlorobenzo[*b*]furan, with *cis*-elimination proving the more facile. When heated at 100°C in acetic acid the *trans*-isomer gave 2-chlorobenzo[*b*]furan, whereas the *cis*-compound isomerized (77JHC359) (Scheme 1).

Similar 2,3-adducts form with chlorine or bromine in carbon tetrachloride when the reactions are carried out with an iodine promotor and in the presence of light [57FES930; 60LA(631)194]. More polar solvents



SCHEME 1



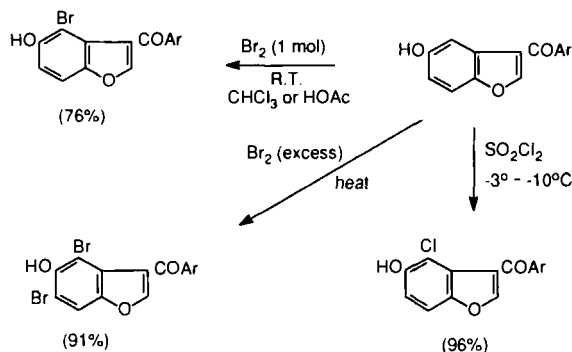
SCHEME 2

and elevated temperatures favor hydrogen halide elimination (48JA1158; 60ACS1233).

Reaction of 2-acetyl-3-acetamidobenzo[*b*]furan with sulfuryl chloride gave the 2-chloro derivative, but the corresponding 2-nitro derivative was transformed under the same conditions into 3-acetyl-2-nitro-2-coumarin (80JHC1125) (Scheme 2). A detailed study of chlorination and bromination of benzo[*b*]furans carrying acyl substituents showed that a 3-aryl group does not prevent attack at C-4 even though it deactivates the furan ring. A 3-carbethoxy group, however, hinders 4-halogenation. An hydroxyl function in the 5-position generally directs halogenation *ortho* to itself (Scheme 3), but when esterified it becomes an electron-acceptor. Halogenation no longer occurs under the same reaction conditions, and may take place in the furan ring (76CHE265; 83CHE1044). Chlorination of 2-acetyl-3-acetylaminobenzo[*b*]furan resulted in *ipso*-substitution; the acetyl group was replaced by chloro [78JCS(P1)419].

With bromine monochloride at 0°C in a variety of solvents, **1** was converted into addition products, the product distribution being a function of solvent. A change in halogenating agent also altered the product ratio. (Scheme 4) Nucleophilic displacement reactions between these products and silver fluoride was found to cause preferential bromine substitution (83G149).

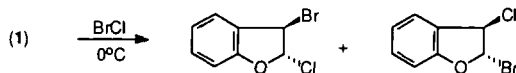
Benzo[*b*]furan is brominated in carbon disulfide and other solvents to give 2,3-adducts [02CB1633; 66JIC437; 71JCS(B)79; 74JCS(P2)1882; 76JCS(P2)266; 77JHC359; 77JHC949; 80JHC1147]. The reactions probably go through the usual Wheland intermediates at C-2 and, depending on the temperature, there can be attack by bromide ion at the 3-position giving the *trans*-adduct, at the bromine atom to regenerate **1**, or proton removal from the 2-position to give 2-bromobenzo[*b*]furan (79JOC32). The kinetics of the reaction have been studied (74BCJ1267). At -40°C the *trans*-dibromo product is formed (steric hindrance probably prevents the *cis*-adduct from forming), and it is quite stable at room temper-



SCHEME 3

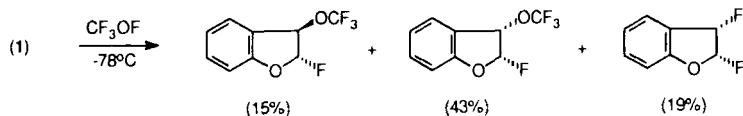
ature. When gently heated, however, an equilibrium is established with benzo[*b*]furan, and heating with acetic acid gives the 2-bromo derivative irreversibly. Base-catalyzed elimination, though, gives rise to 3-bromobenzo[*b*]furan. Use of the polymer-supported reagent *N*-cyclohexylpyridiniumperbromide in dichloromethane also gave the *trans*-2,3-dibromo adduct (89T7869). A recent patent has recommended the use of gallium bromide catalyst with bromine at 15–20°C in the dark for the bromination of **1** (89BRP2213478). Trifluoroxymethane reacted with **1** to give electrophilic addition products [77JCS(P1)2604]. (Scheme 5).

The presence of methyl groups in the 2- and 3-position directs bromination to the adjacent carbon. When both positions are substituted by methyl there is an initial addition process, but the ultimate products are brominated in a side chain. Even 3-methylbenzo[*b*]furan reacted with NBS to give 2-bromo-3-bromomethylbenzo[*b*]furan (48HCA78; 84BAU445). The 2-phenyl derivative of **1** gave a mixture of 3-bromo and 3,6-dibromo



solvent	% yield	% yield
CCl ₄	78	22
CH ₂ Cl ₂	15	85
MeNO ₂ - CCl ₄	17	83
MeNO ₂	5	95

SCHEME 4



SCHEME 5

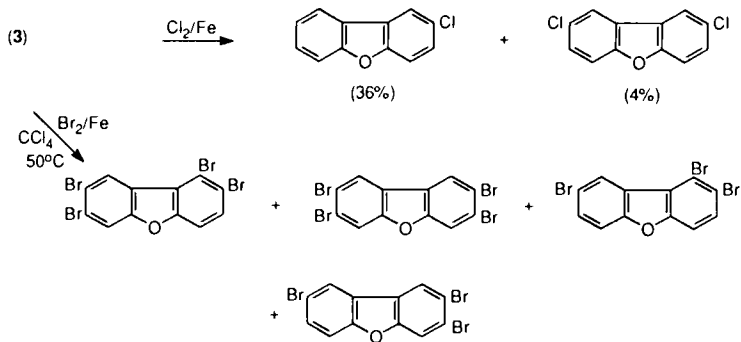
products (64MI1), whereas 2,3-diphenyl **1** was 6-brominated (65MI2). 3-Acetylamino-5-methoxybenzo[*b*]furan gave a 73% yield of the 2-bromo derivative when treated with NBS (87CHE146). Hydroxy groups at the 5- or 6-position of 2- and 3-phenyl derivatives of **1** are sufficiently activating to direct most initial bromination into positions *ortho* to themselves. Thus, the 5-hydroxy-2-phenyl derivative gave an 83% yield of 4-bromo product when treated with one molar equivalent of bromine in acetic acid. Two molar equivalents of bromine led to substitution also in the vacant position of the furan moiety. Esterification of the hydroxy groups changed the substitution pattern to one in which the first bromine entered the furan ring (76CHE265).

When there are electron-withdrawing groups in the furan ring bromination is directed into the fused benzene ring. Esters of benzo[*b*]furan-2-carboxylic acid were brominated at C-5. The free acid would not react, but its anion eliminated carbon dioxide and gave 2-bromobenzo[*b*]furan [01CB770; 37MI1; 74HC(29)1].

b. *Dibenzofuran*. Halogenation of dibenzofuran (**3**) occurs initially in the 2-position, and then at carbon-8 [61JCS4921; 84AHC(35)2]. Both positions are *para* to the oxygen function, and this substitution orientation is common to other benzoxa heterocycles (58JCS4665). If there is an electron-withdrawing group in one ring, halogenation occurs at the 8-position in the other.

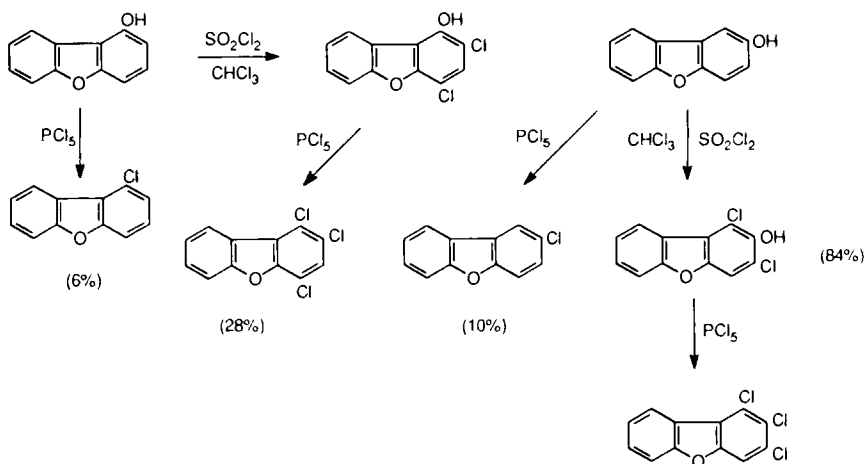
Both bromine in acetic acid and NBS in boiling carbon tetrachloride converted **3** into 2-bromodibenzofuran in good yields, whereas analogous chlorination in acetic acid in the presence of iron powder gave both the 2-chloro and the 2,8-dichloro derivatives (55JOC657). Reaction of **3** with excess bromine in the presence of a Lewis acid catalyst gave a mixture of tri- and tetra-bromo products with the 1,2,7,8- and 2,3,7,8-tetrabromo isomers predominating. When only three molar equivalents of bromine were used, the major products were tribrominated along with a trace of 2,8-dibromodibenzofuran [82H(19)2349]. (Scheme 6) Dioxan dibromide has been used to prepare this last-named derivative (84MI18).

Electron-rich substituents activate positions *ortho* and *para* to themselves. Thus, electrophilic chlorination of 1- and 2-hydroxydibenzofurans



SCHEME 6

gave the 2,4- and 1,3-dichloro derivatives, respectively (Scheme 7) [82H(19)2349], and bromination followed the same pattern (39JA1365). It is possible to prepare a variety of halogenated dibenzofurans by use of combinations of electrophilic and nucleophilic processes. The 2-chloro derivative of **3** is best prepared by reaction of the parent with phosphorus pentachloride [84AHC(35)2], and once some halogen atoms have been introduced electrophilically, such nucleophilic halogenations become even more facile. Some examples are shown in Scheme 7. It was not possible, however, to introduce chlorine atoms into the remote fused benzene ring of hydroxydibenzofurans even when the hydroxy group was acetylated. Either tars were formed or unchanged starting materials were recovered [82H(19)2349].



SCHEME 7

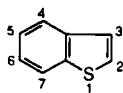
Brief reaction of 3-aminodibenzofuran with chlorine in carbon tetrachloride at room temperature gave the 4-chloro product. After 5 min, a 1:0.4 ratio of 3-amino-4-chloro and 3-amino-1,2,4-trichloro derivatives had formed. Subsequent diazotization and reaction with Cu(I)^{37} Cl gave products with a labeled chlorine in the 3-position (90SC2501). 2-Methoxydibenzofuran was brominated to give the 3-bromo (33%) and a little of the 1-bromo derivative [39JA1365; 84AHC(35)2].

Both 4,6- and 3,4-dimethoxydibenzofurans were brominated at C-1 [84AHC(35)2]. Iodination of **3** follows the same trends as other halogenations (65MI1). Dibenzofuran is lithiated at the 4- and thallated at the 2-position, providing access to 2- and 4-iodo derivatives (57IZV1391).

2. Furans Fused to a Nonbenzenoid Homocyclic Ring

Quaternary ammonium tribromides in methanol-dichloromethane did not brominate the furan ring of 3-methyl-8*H*-cyclohepta[*b*]furan-8-one. Instead, the 7-bromo derivative was formed (92BCJ295).

3. Benzothiophenes



(4)

a. *Benzo[*b*]thiophenes*. Benzo[*b*]thiophene (**4**) is less reactive than thiophene, but it is still very readily halogenated. The fused benzene ring lowers the reactivity of the 2-position by a factor of 10 and raises C-3 reactivity by a factor of 180 [72JCS(P2)97; 81AHC(29)172].

With molecular chlorine in acetic acid in the presence of iodine **4** gave 2,2,3,3,4,5,6,7-octachloro-2,3-dihydrobenzo[*b*]thiophene (80JOC2151), but under milder conditions the products were 3-chloro- (69%), 2,3-dichloro- (28%), and 2-chloro- (3%) benzo[*b*]thiophenes [51JA2614; 51USP2571742; 55JCS1565; 66CJC2283; 68JCS(B)397; 71JCS(B)79]. Addition products are quite commonly formed during chlorination processes; a *trans*-adduct was formed with the 2,3-dimethyl derivative of **4** (ultimately the product isolated from this reaction was 2-chloromethyl-3-methylbenzo[*b*]thiophene [76JCS(P2)266]. Clearly the stabilization from the sulfur atom makes the transition state for 3-substitution more favorable than that for 2-substitution. In the chlorination of 3-bromobenzo[*b*]thiophene, not only was the 2-chloro derivative formed, but also as a conse-

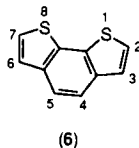
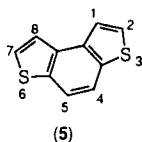
quence of *ipso*-substitution, all of the possible product combinations arising from attack by the displaced bromine [73IJS233].

Directing effects of substituents follow the usual trends with activating groups at C-2 or C-3 favoring attack at the adjacent vacant sites (83S932), while deactivating groups direct the incoming electrophile into the fused benzene ring [71AHC(13)235; 70AHC(11)177].

Controlled bromination of benzo[*b*]thiophene gave the 3-bromo derivative; excess halogen gave the 2,3-dibrominated product [67AJC313; 70AHC(11)177; 71JCS(B)79; 81H(15)1285]. When the 2- and 3-positions are blocked the fused ring is substituted. Thus, 2-bromo-3-methylbenzo[*b*]thiophene was converted into a 4:1 mixture of the 2,6- and 2,4-dibromo derivatives [85H(23)2391], whereas the 2,3-dimethyl compound was mainly 6-brominated (66BSF3055), as was the 2,3-dibromo derivative of **4** and its 5-methyl analogue [70JCS(C)1949]. The 6-position in the fused ring is more reactive toward electrophiles than the 5-position [90AHC(47)98].

Certainly bromination is a more selective reaction than chlorination with **4** [67AJC313; 71JCS(B)79], and the stronger preference for 3-bromination is evident even in the presence of substituents such as 2-phenyl (66JMC551), 2-*t*-butoxycarbonylamino (83S932), 2-fluoro (63JOC1420), and 5-bromo (65NKZ1067). Bromination of both 2- and 7-methyl derivatives of **4** occurred mainly at C-3 [53JA3278; 65NKZ853; 66AJC1909, 66BSF3618]. Only when the 3-position is blocked does high-yield 2-bromination occur [52JA2185; 67NKZ755; 72JCS(P1)1404; 83S932].

The nature of the brominating medium has an influence on reaction products. Although there is no need for strongly acidic reagents, a buffer is frequently added to adsorb HBr [81H(15)1285]. When 2,3-dibromobenzo[*b*]thiophene was brominated in sulfuric acid with silver sulfate present, a small amount of the 4-bromo (but none of the expected 5-bromo) derivative was observed [70JCS(C)1949].



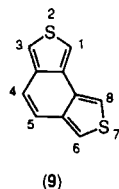
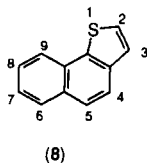
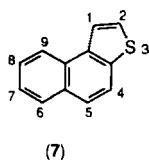
The dithienobenzene (**5**) was converted into a 5:3 mixture of 2- and 1-bromo products. In contrast, the isomer (**6**) gave mainly 2-brominated material, but further bromination took place successively in the 7-, 3-, and 6-positions [77CS(12)97]. This preference for α -bromination contrasts

with the behavior of **4**, but it can be rationalized in terms of conjugation in the transition state with the sulfur in the remote ring.

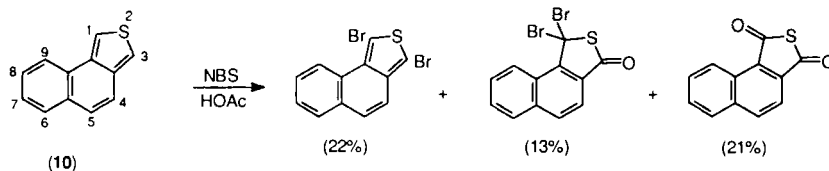
Iodination of **4** with molecular iodine in the presence of mercuric oxide formed the 3-iodo derivative [52JA4951; 66CJC2283]. Iodine in tetrahydrofuran oxidatively cyclized β -(3-benzo[*b*]thienyl)- α -mercaptoacrylic acids rather than iodinating the thiophene ring [70JCS(C)2431].

b. *Dibenzothiophene*. Dibenzothiophene was initially brominated in the 2-position [74AHC(16)181]. The 4-halogenated derivatives are better prepared from the 4-lithio derivatives than from Sandmeyer reactions (57JOC523). Reaction of the lithium derivative with cyanogen bromide or tosyl chloride gave the 4-bromo (60%) and 4-chloro (63%) products (90JHC1737). Attempted fluorination of dibenzothiophene with xenon difluoride in acetonitrile or methylene chloride gave only sulfoxides and sulfones (83MI1).

c. *Naphthothiophenes*. In both naphtho[2,1-*b*]- (**7**) and [1,2-*b*]-thiophene (**8**) initial bromination occurred at C-2 [69JCS(C)537; 73JCS(P1)2956; 77JCS(P1)63]. Calculations suggest that **7** should undergo electrophilic attack at the 1-position, and at the 3-position in the isomer (**8**) [73JCS(P1)2956]. The observation that bromination actually takes place at the 2-positions could be because of steric hindrance, or it may be that the calculations are deficient [69JCS(C)1274]. When there is a methyl group at the 2- or 3-positions of **8** bromine enters the adjacent site, as it does with the 3-formyl derivative, but when both sites are blocked, as in the 2,3-dimethyl- and 2-bromo-3-methyl-derivatives, bromine in acetic acid gave the 5-bromo products [77JCS(P1)63]. The strongly electron-withdrawing 2-carbethoxy substituent also favored the 5- rather than the 3-brominated product [73JCS(P1)2956].



d. *Benzo[*c*]thiophenes*. When fusion is at the *c*-bond, as in benzo[1,2-*c*: 3,4-*c'*]dithiophene (**9**), treatment with one molar equivalent of NBS gave a 6:6:1 ratio of 1-bromo-: 3-bromo-: 1,3-dibromo- products. With three equivalents of NBS the products were the 1,3,6-tribromo- (48%) and 1,3,6,8-tetrabromo- (30%) derivatives with no attack in the homocyclic



SCHEME 8

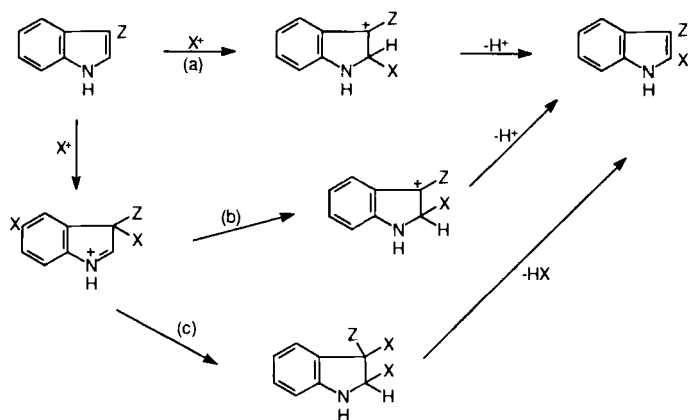
ring (84JOC1027). With naphthalene fused at the *c*-bond as in **10** the products of bromination with bromine in chloroform were the 3-bromo- and 1,3-dibromo- derivatives. The use of NBS in acetic acid, however, gave a mixture that included a thiolactone and thioanhydride, probably derived from 1- and 3-dibromination products (82JOC1018). (Scheme 8)

4. Indoles and Other Benzopyrroles

The halogenation of indoles [70MI1; 72HC(25-2)127; 74MI2; 84MI15; 90AHC(47)181] and isoindoles [81AHC(29)341] has been discussed in a number of articles. The first halogen enters the 3-position if vacant, followed by 2-halogenation. Positions 5 and 6 are then substituted, although substituents can modify this regiochemistry [82JCS(P2)909]. Highly chlorinated indoles are reported to be moisture sensitive and prone to form carbonyl compounds. One might expect ready 3-halogenation of isoindole (benzo[*c*]pyrrole) because the Wheland intermediate generates a true 6 π -benzenoid system.

a. *Indoles*. Unlike dihalogenated indoles, the 2- and 3-monohalogeno compounds are not particularly stable. Although 3-halogenation is believed to follow a simple electrophilic process (but see discussion of *N*-halogenation below), when this position is blocked attack can occur at carbon-2. Of the variety of possible mechanisms that could account for this (see Scheme 9) only the addition–elimination pathway [pathway (c)] has not been observed. When Z is an alkyl or acyl group *ipso*-attack is followed by rearrangement [pathway (b)]. When the benzene ring is activated, route (a) is the preferred option [78CC779; 86H(24)2879].

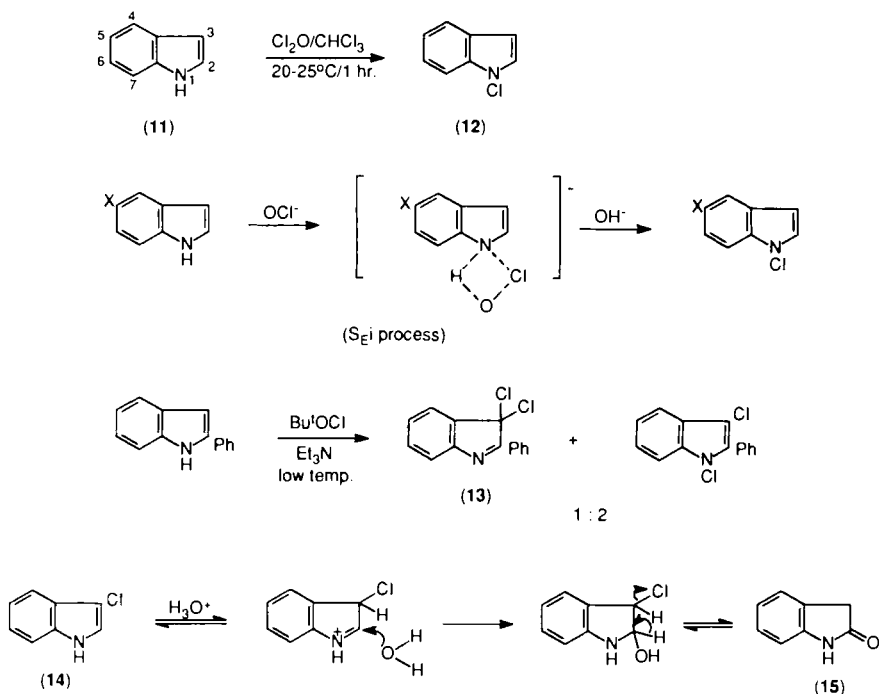
N-Chlorinated indoles have been implicated in a number of processes that ultimately lead to the more stable C-chloro derivatives. When indole (benzo[*b*]pyrrole; **11**) was treated with sodium hypochlorite the initially formed product was 1-chloropyrrole (**12**) which rearranged with base to 3-chloropyrrole (75CC482; 78JOC2639; 81JOC2054); 2-methylindole gave a 2:1 mixture of 1,3- and 3,3-dichloro derivatives [81JOC2054;



SCHEME 9

86H(24)1311], and 2,3-dimethylindole also formed an *N*-chloro derivative under similar conditions [72T2749]. Chlorine monoxide in chloroform gave a 90% yield of **12** when reacted at room temperature with **11** (65NEP6409386). A recent study of the action of hypochlorite on 5-substituted indoles points to the operation of competitive S_E2 and S_Ei mechanisms. The latter gives *N*-chloro products and is favored by electron-withdrawing substituents, which increase the acidity of the NH group. The S_Ei process (Scheme 10) is independent of pH, but it occurs best at high pH when only low equilibrium amounts of hypochlorous acid are present. The alternative S_E2 process, which forms 3-chloroindoles, occurs when indoles or their anions react with hypochlorous acid. Excess hypochlorite further transforms these 3-chloroindoles into 1,3-dichloro products. Electron-donating substituents and low pH favor 3-chlorination, and although sodium hypochlorite is known to promote the 1,3- \rightarrow 3,3-rearrangement it is not necessary for the reaction [86H(24)1311]. It is possible that 3-haloindolenines (**13**) may be implicated in indole halogenations. They can be made with a number of reagents under controlled conditions [72HC(25-2)127; 80CJC808, 80H(14)867; 81JOC2054]. (Scheme 10)

The *N*-arylsulfonylation of 2-arylindoles using arylsulfonyl halides under phase-transfer conditions was accompanied by some 3-halogenation, assumed to be electrophilic in character [83JCS(P1)2417]. In warm alkali, chlorine converted indole into the 3-chloro derivative (**14**), but in acidic conditions the product is protonated with subsequent formation of oxindole (**15**) [70MI2; 72HC(25-2)127] (Scheme 10). Solvolysis of 2-chloroindole in acidic medium also gave **15** (74MI2). These processes make it difficult



SCHEME 10

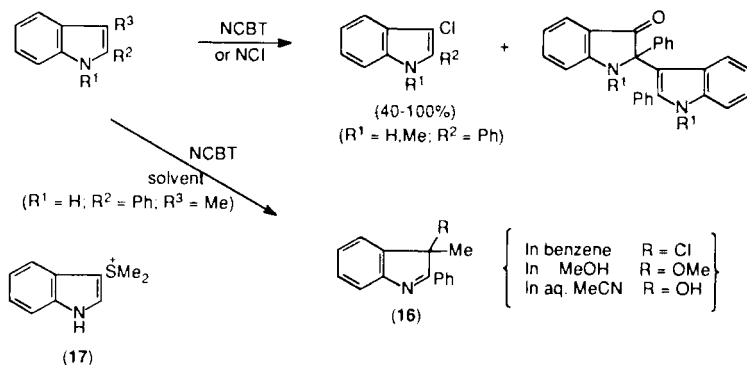
to prepare derivatives of **14** free of oxygen-containing by-products by traditional halogenation methods [64JOC1206; 66JOC2627; 69JA7333; 70CJC422, 70MI1; 72T2749; 86H(24)2879]. Sulfuryl chloride has proved a synthetically useful reagent for preparing 3-chloro- and 2,3-dichloroindoles, usually as mixtures though [66JOC2627; 86H(24)2879]. The same reagent 3-mono- and 2,3-di-chlorinated 4,7-dichloroindole [89H(29)1663] and converted naphtho[2,3-*f*]indole-5,10-dione and naphtho[2,3-*e*]indole-4,9-dione into the 3-chloro derivatives in high yield [89ZVK129]. Even ester groups at C-2 do not prevent 3-chlorination, although they do promote some reaction in the fused benzene ring [82CHE932]. A 6-methoxy group elicits a mechanistic change when it leads to about 30% 2-chlorination, a pathway that becomes even more important with 4,6-dimethoxyindole [82JCS(P2)909].

As with the pyrroles, *N*-chloroamides have been widely employed in indole chlorination [66JOC2627; 80H(14)867; 81JOC2054]. Chloroindolenines may be isolated under controlled conditions [80H(14)867; 81JOC2054]. 2-Phenyl-, 1-methyl-2-phenyl- and 3-methyl-2-phenyl-indoles were converted by 1-chloroisatin (NCI) into the 3-chloro derivatives

(82JOC4895). The action of 1-chlorobenzotriazole (NCBT) with the first two substrates was similar, but the product with 3-methyl-2-phenylindole was very much solvent dependent. Presumably the initially formed 3-chloro derivative (**16**; R = Cl) reacted with methanol or water. In contrast to the NCI reaction, an electron-transfer process with NCBT was suggested on the evidence of chemical and electrochemical studies; differences between the two reagents are presumably a consequence of the differential mobility of the chlorine atom (82JOC4895) (Scheme 11). Indole-3-carboxylic acid was transformed by *N,N*-dichlorourethane into 3,3,5-trichloro-oxindole (via **14** and **15**) (68JOC4440; 70CJC422). Free radical halogenation of protected L-tryptophan with NCS or NBS gave the 2-chloro (55%) and 2-bromo (83%) derivatives (83TL5555).

Selective chlorination (and bromination) is possible from one of the possible electrophilic sites (S, Cl) in the chlorosulfonium intermediate, $\text{Me}_2\text{S}^+\text{Cl}$, when indoles are treated with trimethylchlorosilanes and sulfoxides. A typical reaction gave **14** (35%) and 3-sulfoniumindole (**17**) (37%). Increased steric interactions induced by increasing the size of the sulfoxide improved the yield of **14** to 53%, whereas a larger 2-alkyl group in indole had the same effect. Skatole (3-methylindole) was smoothly 2-chlorinated by this method, whereas 1-methylindole behaved like the parent [89JCR(S)182]. These reagents have been employed to chlorinate and brominate indole alkaloids (89SC3415).

Syntheses of chloroindoles via organometallic derivatives have been largely confined to the use of thallium derivatives. The processes are quite general, serving equally well for bromo and iodo derivatives [84H(22)797; 87H(26)1173; 89JAP(K)0131762, 89JAP(K)0131763]. 7-Chloroindoles have been prepared using a strategy that employed a 1-acetyl substituent in

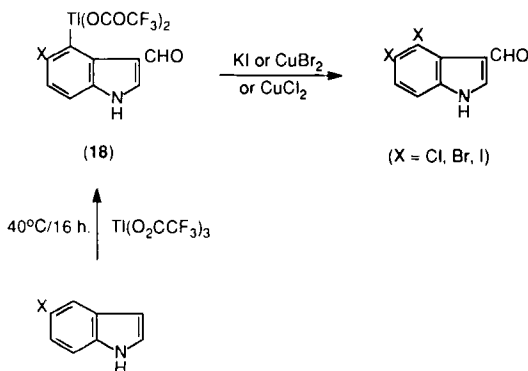


SCHEME 11

indoline to direct thallation into the 7-position (the acetyl group coordinates with the metal). Reaction with copper(II) halides gave the 7-halogenoindolines in 42–74% yields. Oxidation to the indole before removal of the acetyl group completes the synthesis [85H(23)3113; 87CPB3146]. The method has been applied to the preparation of 5,7-, 6,7-, and 4,7-dihalogenated indoles. Thallation of 5-iodo, 5-chloro-, and 5-bromo-3-formylindoles (**18**) occurred in the 4-position, thereby providing a route to 4,5-dihalogenated products (Scheme 12). From 3-formyl-6-halogenated indoles (made from the 6-amino derivatives) 4,6-dihalogenoindoles are similarly available in 70% yields [87H(26)2817]. These thallation procedures have been combined with standard halogenation methods to provide a wide range of tri- and tetra-halogenoindoles [89H(29)1663].

At high copper(II) chloride:indole ratios the pyrrole ring of 2-methylindole was chlorinated in yields approaching 92%. This reaction is believed to involve radical cations of indoles formed in an electron-transfer process. At low copper(II) chloride:indole ratios dimers were formed [86JCS(P1)2305].

Nucleophilic processes that generate chloroindoles are largely confined to the displacements of oxy functions and Sandmeyer reactions of diazonium salts [81H(15)547]. A low yield of 2-chloroindole was obtained by a reaction sequence that involved treatment of oxindole with phosphoryl chloride, and then treatment of the Vilsmeier salt with sodium bicarbonate [66JOC2627; 86H(24)2879]. It is, however, much better to prepare this compound from 2-lithioindole (92JOC2495). With phosphoryl chloride and dimethylformamide ethyl 1-hydroxyindole-2-carboxylate failed to give the expected 3-formyl derivative. Instead there was a 50% yield of the 3-chloro derivative (84CPB3678). Diazonium salts have been used as precursors in

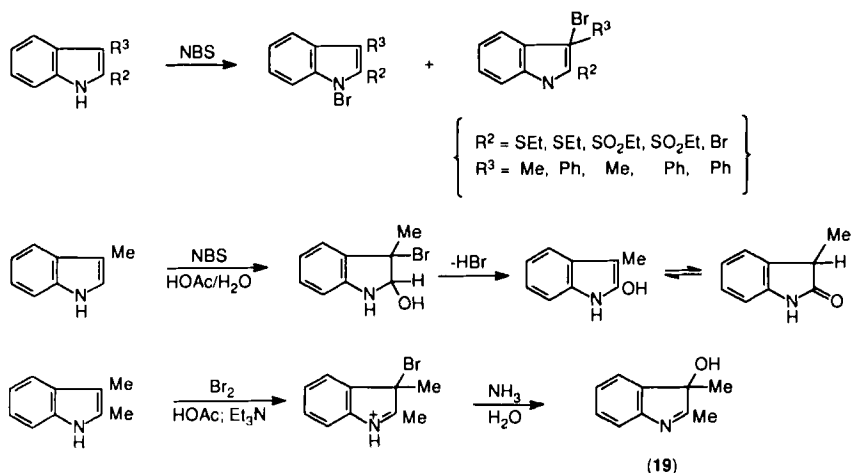


SCHEME 12

the preparation of 4- [82JAP(K)57/159765] and 6-chloroindole derivatives [87H(26)2817].

A number of bromination processes probably proceed via the *N*-bromoindoles and 3-bromoindolenines [74H(2)565]. Both of these species are capable of brominating a 3-substituted indole in the 2-position, whereas in aprotic solvents a 3-bromine can migrate to the 5- or 6-positions [60JA5918; 74H(2)565]. The indolenines can also react with solvent to give oxindoles. These processes are illustrated by the reaction of NBS in aqueous acetic acid with 3-methylindole [72HC(25-2)127] (Scheme 13), and NBS in *t*-butanol with indole or 3-bromoindole, which are ultimately converted into isatin [89JCS(P1)2009]. When 2,3-dimethylindole was similarly treated, and the product hydrolyzed in aqueous ammonia, an hydroxyindolenine (**19**) was isolated (80CJC808). When anhydrous or aprotic solvents are used it is possible to isolate the bromoindoles (88MI2).

3-Bromoindole has been directly prepared using such diverse reagents as pyridinium perbromide [72HC(25-2)127; 86H(24)2879]; trimethylphenylammonium tribromide [72HC(25-2)127]; dioxan dibromide [63CJC2399; 67BSF1294; 72HC(25-2)127]; bromine in aqueous alkali (54ZOB1265), in carbon disulfide (44LA1), chloroform (85CHE786), or dimethylformamide (82S1096); bromosulfonium species [89JCR(S)182]; NBS in anhydrous, aprotic solvents (88MI2), or supported on microporous solids (86TL1051; 91MI2); 2,4,4,6-tetrabromocyclohexa-2,5-dienone [72JCS(P1)2567]; *t*-butyl bromide in dimethyl sulfoxide (82G535), and trimethylbromosilanes with sulfoxides [89JCR(S)182]. Yields of 3-bromoindole vary from around



SCHEME 13

60% for molecular bromination in aqueous alkali, to 88% for tetrabromocyclohexa-2,5-dienone, to 96% for bromine in dimethylformamide. Solid support bromination of indole was unsuccessful because the heterocycle polymerized (86TL1051; 88MI2).

The use of NBS in aqueous acetic acid is contraindicated as mentioned above. The products are more likely to be oxindoles or bromoindolenines [60JA5918; 64JOC1206; 77H(6)1680; 82G535; 84TL3099], but in aprotic media bromoindoles are formed. Skatole was converted by *N*-bromophthalimide in benzene into a moderate yield of 2,6-dibromo-3-methylindole (45JGU332); NBS in acetic acid (60JA5918; 64JOC1206) or in the presence of benzoyl peroxide was an improvement (83TL5555) and it was recently reported that NBS supported on silica gel gave a 96% yield of 2-bromoskatole within half an hour. With two molar proportions of NBS the 2,6-dibromo product was produced in 77% yield, and 2-methylindole similarly formed the 3-bromo (98%) and 3,6-dibromo (95%) derivatives (86TL1051).

Both 3-bromo- and 3-iodo-indoles have been selectively prepared by titrimetric addition to the heterocycle of the halogen dissolved in dimethylformamide. The mildly basic solvent is probably responsible for trapping the generated hydrogen halide (82S1096).

Provided that the 3-position is vacant, it is brominated almost exclusively in the presence of a variety of 2-substituents whether in neutral medium or conditions that generate the anion of indole [76CI(M)220; 82G535, 82S1096; 86H(24)2879, 86TL1051; 88MI2; 92S743]. Once C-3 has been substituted, further bromination can occur in the 6-position [76CI(M)220], although the reactivities of positions -5 and -6 are probably fairly comparable. A donor group in the 3-position and an electron-attracting group at C-2 can cause preferential 5-bromination (81MI1), but 1,2,3,7-tetramethylindole brominated at C-6 (71CHE1406).

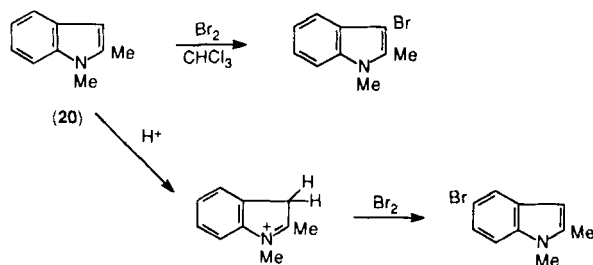
Although electron-attracting groups in the 2-position will seldom prevent 3-bromination, they also favor some substitution in the homocyclic ring. Thus methyl indole-2-carboxylate gave a mixture of 3-bromo- and 3,5-dibromo- products (80CHE887), and there are other analogous examples (82CHE932). Electron-withdrawing groups in the benzene ring do not alter the preference for 3-bromination, but they do decrease reaction rates (44LA1; 80CHE887; 85CHE786). An acyl or aroyl group in the 1-position also decreases the reactivity of the pyrrole ring. This effect can be noticed when the orientation and rates of bromination of 5-vinylindole and its 1-methyl and 1-acetyl derivatives are compared. Bromine entered both the 3-position and the vinyl group with the pyrrole ring being the more reactive site except in the 1-acetyl compound (87CHE271). The methyl ester of 1-carboxy-2-methylindole was brominated at the 3-position in 93% yield

by NBS in carbon tetrachloride. In the presence of benzoyl peroxide, though, lateral bromination took place exclusively (92S743). The ethyl ester of indole-5-carboxylic acid was preferentially 3-brominated, but NBS converted 4,7-dichloroindole into the 2,3-dibromo derivative, and 3,4,7-trichloroindole into the 2-bromo compound [89H(29)1663].

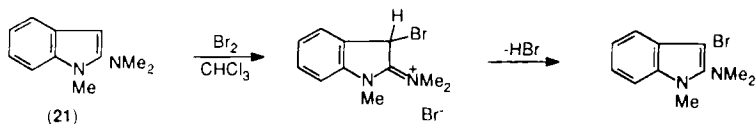
When 1-methyl-, 1,2- and 1,3-dimethyl-indoles were oxidized on a platinum electrode in methanolic ammonium bromide solution, in addition to the oxidation products, products of nuclear bromination at the 3- and 5-positions were observed. 1,2-Dimethylindole (**20**) gave 3-bromo-1,2-dimethylindole (81CCC3278) [bromine in chloroform gave the same product (85CHE786)]. In acidic conditions the amidinium cation formed from **20** was brominated in the 5-position (Scheme 14). Acylated 2-aminoindoles reacted similarly in neutral media to give 3-bromo derivatives and when protonated to give 5-bromo products. Bromine in chloroform transformed 1-methyl-2-dimethylaminoindole (**21**) into the 3-bromo derivative (85CHE782) (Scheme 15).

The presence of phenyl (74T2123; 80CHE887), substituted alkyl (75CPB2990; 86TL1051; 91MI2), or halogen [86H(24)2879] groups at the 3-position does not prevent 2-bromination from occurring with some facility. 3-Phenylindole gave a small amount of 3,5-dibrominated material as the minor product of bromination. Indeed, it is only when there are bulky groups at both 1- and 3-positions that attack is directed into the fused benzene ring, usually at the 6-position (80CHE887). Acyl groups at C-3, however, frequently direct at least a proportion of any bromination into the homocyclic ring (68MII).

Bromine in acetic acid converted 3-formylindole into low yields of the 5- (6%) and 6-bromo (3%) derivatives along with smaller amounts of 5,6-dibromo and 2,3,5,6-tetrabromo species (67G1304). 3-Acyl-2-aminoindoles (**22**) displayed high selectivity for 6-halogenation (Scheme 16), but at the same time *unco*-substitution of the acyl group can occur,



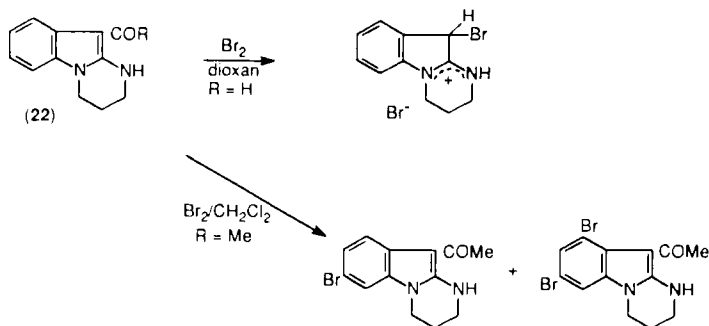
SCHEME 14



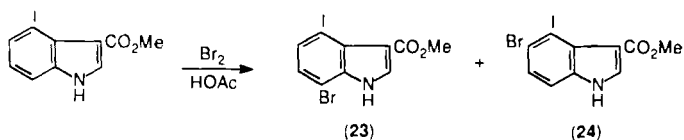
SCHEME 15

especially if it is formyl (90CHE416). Bromine in acetic acid converted methyl 4-iodoindole-3-carboxylate into a mixture of **23** (9%) and **24** (66%) [87H(26)2817] (Scheme 17). A 3-cyanomethyl group did not prevent 2-bromination (and some 2,6-dibromination) by NBS on silica gel. Attempts to prepare polybromoindoles by this method were unsuccessful because of slow reaction rates and the formation of complex mixtures. With tryptamine the primary amino group was oxidized, but this problem could be overcome by brominating the cyanomethyl analogue, and then reducing it later to aminoethyl. 3-Formylindole was not affected by solid-support bromination (86TL1051).

When indoles are brominated in acidic media the protonated heterocycles have reduced reactivity in the pyrrole ring. Under these conditions it is not uncommon for bromination to take place preferentially in the 5-position. Bromine in sulfuric acid with silver sulfate converted 2-methyl- and 2,3-dimethyl-indoles into the 5-bromo derivatives in around 75% yields (65KGS632; 80CHE887). It is much more difficult to make 6-bromoindoles, although this can be achieved in the presence of suitable substituents. One useful approach utilizes regioselective bromination of an indoline. In neutral or acidic solution indoline brominates *para* to the amino group (i.e., at C-5). To favor *meta* (or 6-) substitution the method for cationic bromination of aromatic compounds ($\text{Br}_2\text{--H}_2\text{SO}_4\text{--Ag}_2\text{SO}_4$) is employed, and with 2,3-dimethylindole gave a 50% yield of the 6-bromo derivative



SCHEME 16



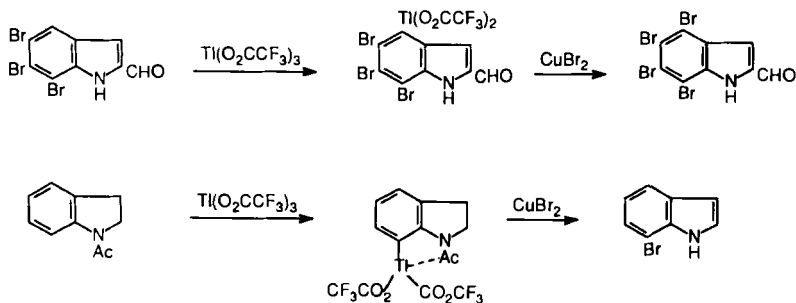
SCHEME 17

(65KGS632). In general this approach has only produced moderate yields, and the requirement for the use of 97% sulfuric acid renders workup difficult. Fluoroantimonic acid seems to be an improvement. Yields of up to 57% of 6-bromo products have been reported free of the traces of the 5-isomers still formed in 97% sulfuric acid (83JHC349).

The use of mixtures of trimethylbromosilane and dimethyl sulfoxide to brominate indoles is more successful than analogous chlorinations since the bromine atom increases the rate of transformation of $\text{Me}_2\text{S}^+\text{OSiMe}_3$ to $\text{Me}_2\text{S}^+\text{Br}$ and shows a stronger electrophilic character than the chloro intermediate. Sulfonium products do not form in such reactions [89JCR(S)182].

Preparation of bromoindoles by replacement of metallic substituents have included oxidation of indolylmagnesium bromide by *p*-nitrobenzoic acid to give 3-bromoindole (67BSF1294), thallation procedures (illustrated in Scheme 18; also applied to the synthesis of chloroindoles) [85H(23)3113; 86H(24)3065; 87CPB3146, 87H(26)2817; 89H(29)1163], and the use of lithium derivatives. The thallation reactions provide access particularly to 4- and 7-bromoindoles. Quenching the protected 2-lithium derivative of indole with 1,2-dibromotetrachloroethane gave an 87% yield of 2-bromoindole (92JOC2495).

Conversions of 2-oxo groups to bromine have been reported [86H(24)2879; 88H(27)1585]. The Batcho-Leimgruber indole synthesis



SCHEME 18

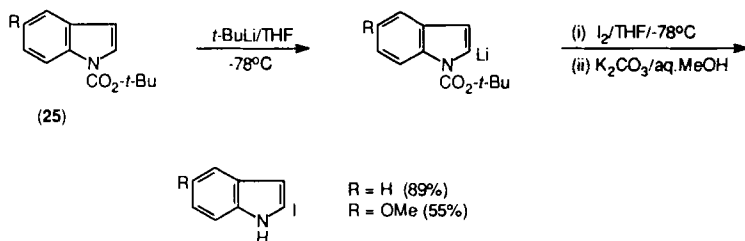
gave 4- (70%), 5- (47%), 6- (62%), and 7-bromoindoles (29%) for a study of metal-halogen exchange (86JOC5106). Sandmeyer reactions have been used to make some 4- [81CPB3145; 85CPB3696] and 6-bromoindoles [87H(26)2817].

Direct iodination of indole with a variety of reagents gave rise to 3-iodoindole. Iodine (particularly in dimethylformamide) (82JOC757; 82S1096), iodine and potassium iodide [86H(24)2879], and iodine monochloride [59JOC117; 72HC(25-2)127] are the most frequently reported reagents. Iodine was found to form a black 1 : 1 charge-transfer complex with indole in chloroform at -20°C [61N(L)168]. Oxidative procedures, too, are not uncommon. 3-Iodoindole was prepared by heating indole in an autoclave with an alkali metal iodide in acidic solution under oxygen [89JAP(K)01/102061]. Further iodination of 2-iodoindole to the 2,3-diiodo derivative was achieved in 82% yield using iodine and potassium hydroxide in dimethylformamide (92JOC2495).

In common with a number of heterocyclic iodinations, kinetic effects are found in the iodination of indole and 2-methylindole [68AC(R)1435]. When the substituent effects for the reaction are examined it is clear that any resonance effects from the fused benzene ring are only poorly relayed to the reactive 3-position, and the rates appear to be controlled by inductive effects. A 5-methyl group was more activating than 5-methoxy [69AC(R)799].

Iodine in the presence of morpholine converted 1-methoxyindole into the 3-iodo derivative in 27% yield (85CPB5147). When treated with diiodoacetylene, an indolylmagnesium halide gave 3-iodoindole in 83% yield (54CB1148).

Introduction of an iodine to C-2 of indole can be accomplished using lithium derivatives. Since direct iodination tends to give mixtures it is essential to activate the 2-position at the expense of the inherently more reactive 3-position. This has been done by lithiating 1-*t*-butoxycarbonylindoles (**25**) and then converting them into iodo derivatives before deprotection (85JHC505) (Scheme 19). Alternatively carbon dioxide can be used



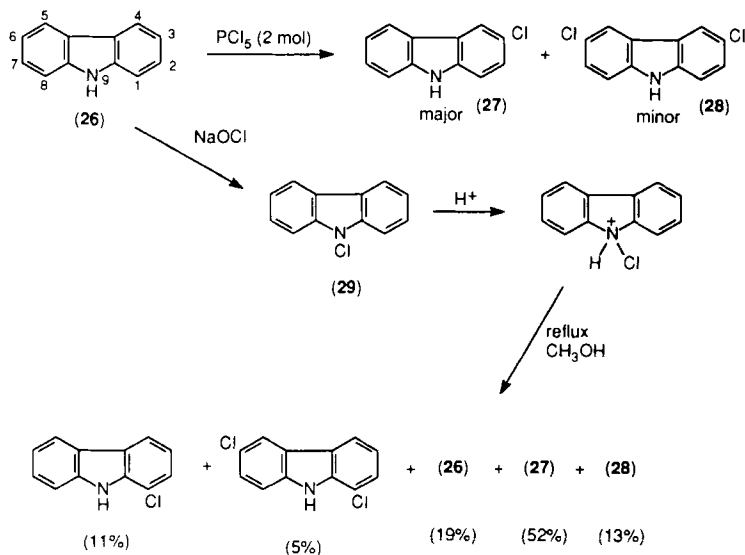
SCHEME 19

as both an activating and a protecting group (85TL5935). A 90% yield of 2-iodoindole has been obtained in this way (92JOC2495). Thallation procedures have been mentioned above [85H(23)3113; 86H(24)3065; 87CPB3146, 87H(26)2817], as have methods that convert diazonium salts into iodoindoles [81CPB3145; 85CPB3696; 87H(26)2817].

There have been few reports of indole fluorination. 2-Methylindole was largely destroyed by cobalt(V) fluoride treatment, giving perfluorocyclohexane and perfluoromethylcyclohexane among the products [70MI2; 72HC(25-2)127]. 4-Fluoro-3-indoleacetonitriles have been prepared from the diazonium fluoroborates (85CPB3696).

b. *Carbazoles*. In carbazole (**26**) there are no pyrrole carbons free for halogenation. The NH group directs electrophilic attack most readily into its *ortho* and *para* positions [84AHC(35)83, 84MI15]. Partial rate factors for chlorination have been quoted as $f_3 > 10^8$, $f_1 > 10^7$. For 9-acetylcarbazole the corresponding positional reactivity orders were $3 \gg 2,4 > 1$; the acetyl group presumably reduces reactivity at the vicinal ring position [66JCS(B)521]. Chlorination, then, occurs with most facility at the 3-position (67KKZ63), but it is difficult to avoid mixtures of mono- and poly-chlorinated derivatives with the usual reagents such as sulfuryl chloride, chlorine, or NCS. With phosphorus pentachloride in 1,2-dichloroethane, a mixture of 3-chloro- and 3,6-dichloro-carbazoles was formed, but under carefully controlled conditions (2 mol of phosphorus pentachloride at 60°C) the major product was 3-chlorocarbazole (**27**). Increasing the ratio of chlorinating reagent to substrate to 3:1 led to a good yield of the 3,6-dichloro derivative (**28**). 9-Methylcarbazole reacted similarly (85CHE542) (Scheme 20).

When **27** was treated at room temperature with sodium hypochlorite at pH 12 in alkyl halide solvents the 9-chloro derivative (**29**) was formed in 63–95% yields. Refluxing in methanol induced rearrangement to products chlorinated in the fused benzene rings (87JOC173) as a consequence of acid-catalyzed rearrangement analogous to that observed with 1-chloropyrrole (82JOC1008) (Scheme 20). Carbazoles are known to protonate on the nitrogen, and the cation that is formed is the source of positive chlorine for subsequent electrophilic chlorination, initially in the 1- and 3-positions. Once monosubstitution has occurred the next halogen enters the 6-position [84AHC(35)83]. Treatment of 1-chloro-9-methylcarbazole with N-chlorobenzotriazole gave 1,6-dichloro-9-methylcarbazole (80%) (87JOC173). Chlorine in carbon disulfide converted carbazole into the 3,6-dichloro derivative in high yield, whereas sulfuryl chloride has been recommended for the efficient preparation



SCHEME 20

of **27**; the latter reagent can, however, give polychlorinated products (75MI2). Chlorine has also been introduced nucleophilically via a Sandmeyer process [84AHC(35)83].

As commented recently [90AHC(47)1], bromine in pyridine was reported to give "a truly remarkable 100% of 3-substitution and 7% of 1-substitution" (67KKK63). The use of 1,3-dibromo-5,5-dimethylhydantoin gave a 37% of 3-bromocarbazole (51MI1), and, provided the temperature was kept low, bromine in pyridine also gave mainly the same product. In hot pyridine and in carbon disulfide though, the 3,6-dibromo-, and in hot acetic acid the 1,3,6,8-tetrabromo- derivatives were formed [84AHC(35)83]. A recommended reagent for the specific synthesis of 3-bromocarbazole is NBS in the presence of benzoyl peroxide (75MI2), but NBS in association with a solid support may be even better. It has been reported that one molar equivalent of NBS on silica gel gave a 61% yield of (mainly) 3-bromocarbazole; two equivalents gave 90% of 3,6-dibromocarbazole; four equivalents gave 87% of the 1,3,6-tribromo derivative with only a trace of tetrabromocarbazole, which was formed very slowly with excess NBS. 9-Ethylcarbazole behaved similarly, although more severe competition between mono- and di-bromination was evident. Comparative yields of 9-ethyl-3-bromo-, -3,6-dibromo-, and -1,3,6-tribromo- products were 48, 83, and 100% respectively

[88AX(C)1800; 91MI2; 92T7479]. Tetrabromocarbazole can be made in good yield only if a more powerful brominating agent (e.g., 1,3-dibromo-5,5-dimethylhydantoin) is used in association with an acidic solid support (91MI2).

Reaction of 9-vinylcarbazole with bromine in benzene or ethanol gave the 3,6-dibromo derivative [84AHC(35)83]. Pyridinium bromide perbromide gave a 72% yield of the 3-bromo derivative of 2,4-dimethoxycarbazole. With other reagents mixtures of 3- and 5-bromo-, 3,5- and 3,7-dibromo products were formed. The 5-bromo- and 3,6-dibromo- compounds rearranged quantitatively to the 3- and 3,7-isomers [92JCR(S)2].

Introduction of iodine by Sandmeyer processes has been discussed [84AHC(35)83]. Direct electrophilic iodination is also observed in the 3-position with reagents such as iodine monochloride, iodine-iodic acid-acetic acid, or molecular iodine. With excess reagent, or when C-3 is blocked, 6-iodination follows [84AHC(35)83; 84MI15].

5. *Benzo[b]selenophene*

Benzo[b]selenophene is more reactive than the oxygen and sulfur analogues, but less so than benzo[b]tellurophene, although substituents may modify this to some extent [90AHC(47)181].

Treatment with NCS in carbon tetrachloride converted the parent into the 2,3-dichloro derivative. The 2,3-dibromo compound was made similarly with NBS (74BSF2239), or with bromine in chloroform in the presence of sodium acetate (72CHE13). Monobromination is possible, but generally mixtures form with 2- and 3-bromo products in ratios of the order of 1 : 3 (72CHE13). It was possible to prepare 3-bromobenzo[b]selenophene by reaction of the 2,3-dibromo derivative with butyl lithium followed by hydrolysis. Four moles of bromine gave the 2,3,6-tribromo derivative from benzo[b]selenophene (74BSF2239).

Sandmeyer reaction provides access to 2-iodobenzo[b]selenophene (60MI1); the 4-iodo isomer is made from the lithium derivative (54JA5775).

6. *Benzo[b]tellurophene*

Like tellurophene the fused compound forms 1,1-addition products with halogens (73BSF2468), but further bromination of such a 1,1-dibromo species gave 1,1,2-tribromobenzo[b]tellurophene, which was able to be reduced to 2-bromobenzo[b]tellurophene. The 3-chloro and -bromo compounds were isolated following reaction of triphenylphosphine and the appropriate carbon tetrahalide with 2,3-dihydro-3-oxobenzo[b]tellurophene (80BSB763).

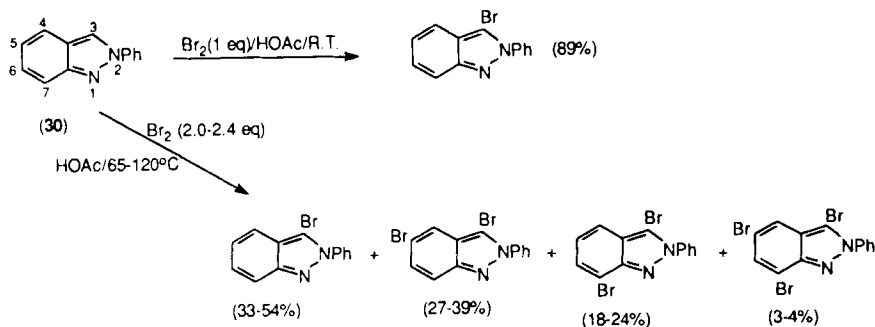
7. Indazoles

Because the reactive 4-position of pyrazole is substituted in indazole (benzo[*b*]pyrazole), substitution by electrophiles occurs by default in the 3-position initially, and then in the 5- and 7-positions of the fused benzene ring (*ortho* and *para* to the N-1). Anionic indazoles always halogenate at C-3 (84MI22).

Chlorine in acetic acid converted indazole at first into 3-chloroindazole, and then into the 3,5-di- and 3,5,7-tri-chloro derivatives. 2-Phenyl-2*H*-indazole (30) reacted similarly to give the 3,5,7-trichloro compound (74MI2). Nitro groups in the homocyclic ring did not prevent 3-chlorination. The 4-, 5-, 6-, and 7-nitroindazoles all gave 3-chloro products in 70–95% yields, and 1-methyl-5-nitroindazole formed the 3,7-dichloro derivative in 70% yield. With chlorine in acetic acid 2-methyl-2*H*-5-nitroindazole gave a 35% yield of the 3-chloro-2-chloromethyl derivative (79JHC1599). Sandmeyer reactions giving chloroindazoles are known [67HC(22)1; 90AHC(48)65].

Partial rate factors calculated for indazole bromination indicate that the benzo derivative is less reactive than pyrazole; a positional reactivity order of 5 > 3 > 7 (in the ratio 10.7 : 6.9 : 1) was obtained [78JCS(P2)865].

When 2-phenyl-2*H*-indazole (30) was brominated in acetic acid with 1 mol of bromine, the 3-bromo derivative was formed in high yield. Subsequently bromine entered the 5- and then the 7-positions (84JOC3401) (Scheme 21). This behavior contrasts with that of the parent 1*H*-indazole, which gave 3,5-dibromoindazole under similar conditions with no apparent discrimination between the two sites, in line with the partial rate factors. Protonated indazole is more prone to 5-bromination than 7-bromination with the 3-position being deactivated in the cation. The anion, however, is most reactive at C-3 (74AJC2343). These differing regiochemistries for



SCHEME 21

the neutral molecule, conjugate acid, and conjugate base probably account for variable results quoted in the literature.

The Hunsdiecker reaction has been used to convert indazole carboxylic acids into the bromo heterocycles [67HC(22)1].

Iodine reacted with the indazole silver salt to give 3-iodoindazole. Reaction of potassium iodide with indazole diazonium salts has been reported on a number of occasions [67HC(22)1; 90AHC(48)65].

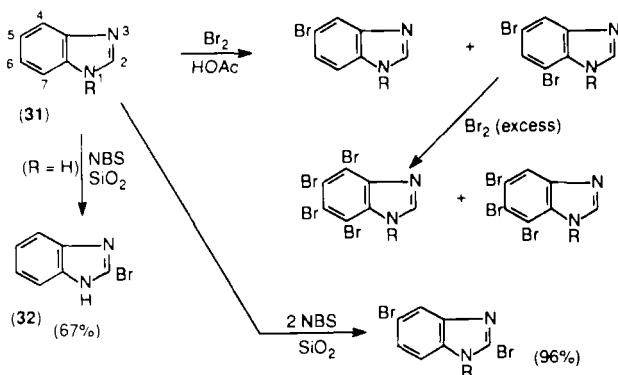
The only approaches to fluorinated indazoles seem to be via the diazonium fluoroborates [77BSF171; 90AHC(48)65]. 5-Fluoroindazole has been nitrated (92PHA22).

8. *Benzimidazoles*

Most electrophilic substitutions in benzimidazole (**31**; R = H) occur primarily in the 5-position. In multiple bromination the order followed, $5 > 7 > 6,4 > 2$, parallels molecular orbital calculations. In benzimidazole itself the 4(7)- and 5(6)-positions are tautomerically equivalent. Fusion of a benzene ring deactivates C-2 to electrophilic attack to such an extent that it is around 5000 times less reactive than the 2-position of imidazole. Strong electron donors at C-5 direct halogenation to the 4-position, whereas electron-withdrawing groups favor C-4 or C-6 substitution (84MI21).

Chlorination of both benzimidazole and its 2-methyl derivative gave 4,5,6-trichloro compounds (74MI2). Such polychlorinated compounds are potent biocides. Use of saturated solution of calcium hypochlorite in acetic acid converted 2,5-dimethylbenzimidazole into an *N*-chloro derivative, which rearranged to give a C-chloro isomer (perhaps 4-chloro). Further reaction eventually gave a tetrachloro product [72JCS(P1)995]. Sulfuryl chloride in acetic acid or HCl in the presence of hydrogen peroxide 4-chlorinated 5-hydroxybenzimidazole (89BAU1494). The most convenient way of introducing chlorine to the 2-position is by reaction of a 2-benzimidazolone with phosphoryl chloride (66RCR122; 80AJC1545). In a recent example 2,5,6-trichlorobenzimidazole was made in 25% yield from 5,6-dichloro-2-benzimidazolone (91MI1). In benzimidazole 3-oxides similar reagents give the 2-chloro products. Chlorine can also displace sulfo and hydrazine groups from the 2-position (84MI21).

Bromination follows the same general pattern as chlorination [78JCS(P2)865] (Scheme 22). A comprehensive kinetic study has demonstrated that benzo derivatives are much less reactive than imidazole itself. Partial rate factors for the bromination of **31** (R = H) were 5-bromination, 6.37×10^7 ; 7-bromination, 2.88×10^6 . For the 7-bromination of 6-bromobenzimidazole the factor was also 2.88×10^6 , confirming that



SCHEME 22

an *ortho*-bromine substituent does not deactivate an adjacent site [78JCS(P2)865; 90AHC(47)181]. This finding is consistent with the prediction (65MI1), and later observation (81JOC1646), that 5-halo compounds can be brominated in the 4-position. The predominant 5-bromination found in these compounds is little affected by substituents as diverse as 2-methyl and 2-trifluoromethyl (73AJC2725, 73MI1; 86TL1051; 87MI1; 91JMC2954). Thus, 2-trifluoromethylbenzimidazole reacted with three molar equivalents of bromine in acetic acid to give a mixture of the 4- (6%) and 5-bromo (65%) products. The reaction was found to be accelerated by added perchloric acid. At 100°C NBS was rather less specific giving 4,5-dibromo (28%), 4,5,6-tribromo (42%), and 4,5,6,7-tetrabromo (13%) derivatives (87MI1).

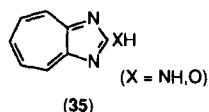
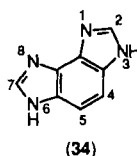
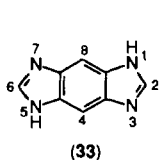
Whereas aqueous and other bromination regimes lead to products with bromine in the homocyclic ring, NBS supported on silica gel forms 2-bromobenzimidazole (32) in the first instance unless the 2-position is already substituted (86TL1051; 88MI2) (Scheme 22). This change in orientation may be a function of the silica holding the 2-position of benzimidazole close to its surface in proximity to the activated NBS (86TL1051). Dioxane dibromide and bromine in acetic acid converted 5-hydroxybenzimidazole into the 4-bromo derivative (89BAU1494). When more reactive heterocycles (2-seleninyl-, 5-methyl-2-seleninyl-, 2-furyl-, 2-thienyl-, 2-pyrrolyl-) are attached to the 2-position of benzimidazole, bromination preferentially affects those highly π -excessive substituents, especially in conditions sufficiently acidic to protonate the benzimidazole (80CHE59; 87CHE1316).

Unless benzimidazoles can react as the anions, when 2-iodination is observed (90JHC673), iodine normally enters the 5-position initially, although N-iodination is also known in alkaline medium. 5-Hydroxybenzimi-

dazole treated with ethanolic iodine and peroxide gave the 4-iodo product (89BAU1494).

2-Fluorobenzimidazole has been made from the corresponding diazonium salt [75MI5; 73JOC3647].

Benzo[1,2-*d*: 4,5-*d'*]diimidazole (33) was halogenated at the 4- and 8-positions (50JCS1515; 52JGU1069; 58JGU2214), whereas benzo[1,2-*d*: 3,4-*d'*] diimidazole (34) was 4- and 5-brominated (73CHE95). The transition states for attack in the observed positions should be more stabilized than elsewhere.



9. Imidazoles Fused to Other Homocyclic Rings

Bromine in pyridine largely dibrominated 2-amino- and 2-hydroxy-1,3-diazulenes (35), although some mono- and tri-bromo products were also detected (88BCJ2690).

10. Benzotriazoles

1-Chlorobenzo[*d*][1,2,3]triazole, prepared by reaction of the parent compound with an acetic acid solution of sodium hypochlorite, is a valuable oxidizing agent for conversion of primary and secondary alcohols into aldehydes and ketones (68CC1305). Benzotriazole can be further chlorinated in *aqua regia* to give an 87% yield of the 4,5,6,7-tetrachloro derivative, with the 1- and 2-methyl derivatives behaving similarly (55JA5105). Under less vigorous conditions the 4,7- (90%) and 4,5- (10%) dichloro compounds were formed (75JOU889). Treatment of the benzotriazole anion with cesium fluoroxysulfate at 0–5°C in acetonitrile gave a 25% yield of 1-fluorobenzotriazole (91T7447).

11. Benzisoxazoles

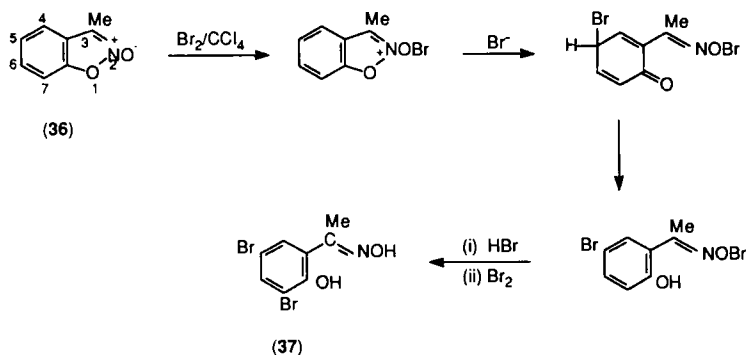
The two isomeric possibilities are 1,2- and 2,1-benzisoxazole. Both are preferentially halogenated by electrophilic halogen in the homocyclic ring, initially in the 5-position, although substituents can modify this behavior [67AHC(8)277]. Nucleophiles attack the heteroring (84MI26).

Although bromination and chlorination of a number of 1,2-benzisoxazoles occurred at C-5 [74RTC139; 79IJC(B)371, 79TL4687; 80ZC18], bromine at room temperature converted the 5-methoxy-3-methyl derivative into a mixture of 4- and 6-bromo products. At elevated temperatures the 4,6-dibromo product was isolated. A series of 3-alkyl-6-hydroxy-1,2-benzisoxazoles were 7-brominated by bromine in acetic acid at ambient temperature, but the 6-methoxy analogues were 5-brominated. At higher temperatures (100–122°C) 5,7-dibromo derivatives were obtained irrespective of the 6-substituent [79IJC(B)371]. Both 3-chloro- and 3-hydroxy-1,2-benzisoxazoles gave 5-bromo products (80ZC18). When there is a susceptible side chain present, as in 1,2-benzisoxazol-3-yl acetic acid, halogenation may occur there for preference [81AHC(29)1].

Bromination of 1,2-benzisoxazole 2-oxides (36) caused ring-opening to give dibromo-oximes (37), a scenario that was also followed in iodination, and contrasting with the nitration behavior, which led to 6-substitution [87JCS(P1)695] (Scheme 23).

3-Chloro-1,2-benzisoxazoles are usually made by nucleophilic displacement of a 3-hydroxy group (67CB3326; 79ZC452; 80ZC18). Yields are commonly between 60 and 80%, and the 3-chloro derivatives can react further with thionyl chloride to form 3,5-dichloro compounds (80ZC18). During the attempted reduction of 3,5-dimethyl-7-nitro-1,2-benzisoxazole with tin(II) chloride in hydrochloric acid, 7-amino-4-chloro-1,2-benzisoxazole accompanied the expected reduction product [67AHC(8)277].

As with the isomers, 5-halogenation of 2,1-benzisoxazoles is favored, but this may be a consequence of an initially formed 4,5-addition product. Such an adduct has been isolated during chlorination [66T(S7)49; 67AHC(8)277]. When 6-nitro-2,1-benzisoxazole-3-carboxylic acid (38)



SCHEME 23

reacted with sodium hypochlorite in methanol the product, 6-chloro-7-methoxy-2,1-benzisoxazole-3-carboxylic acid, indicated that a similar addition-elimination process had taken place across the 6,7-bond [66DIS(B)102, 66TH1] (Scheme 24).

Monobromination of 4-methoxy-3-methyl-2,1-benzisoxazole occurred at C-7, but side-chain bromination was evident with excess reagent (74RTC139).

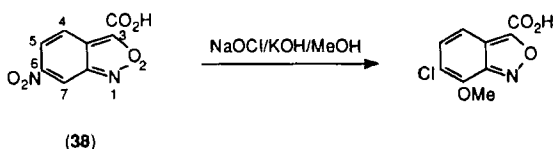
12. Benzoxazoles

Pentachlorobenzoxazole was made by treatment of the parent with excess chlorine and ferric chloride at 80–200°C (72GEP2059725), whereas phosphorus pentachloride converted 5,7-dichlorobenzoxazole-2-thiol into 2,5,7-trichlorobenzoxazole (65NEP6505511). Excess of the latter reagent at 160°C transformed 2-benzoxazolinones into 2-chlorobenzoxazoles in greater than 70% yields (85GEP3334417). Chlorine at lower temperatures (85–90°C) gave ring-chlorinated products only, including 6-chloro- (10%), 4,6- and 5,6-dichloro- (20%), and 4,5,6-trichloro-2-benzoxazolones (60%). Yields were improved by addition of a small quantity of iodine to the reaction mixture (89ZPK1306).

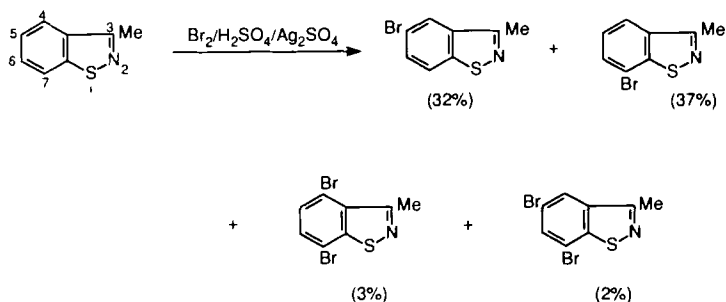
Phosphorus pentachloride at 180°C converted benzoxazole, substituted at C-2 by 3,4-dihydroxy-2-(*p*-nitrophenyl)thiophene, into the 3,4-dichlorinated thiophene derivative only (91JHC1449).

13. Benzisothiazoles

a. *1,2-Benzisothiazoles*. Electrophilic attack occurs preferentially in the fused benzene ring at the 5- and 7-positions. Thus, bromine in sulfuric acid with silver sulfate gave mainly 5- and 7-bromo derivatives, but multiple bromination can also occur (Scheme 25). The 7-chloro (37%) and 7-bromo (40%) derivatives have also been made from the diazonium salts. The above acidic brominating mixture converted 5-bromo-3-methylbenzisothiazole into a mixture of 4,5-dibromo (24%), 5,7-dibromo (10%), and



SCHEME 24



SCHEME 25

4,5,7-tribromo (34%) derivatives; the 4-bromo isomer gave a 96% yield of 4,7-dibrominated product under similar conditions [80JCR(S)197].

Activating groups at the 5-position led to high yields when bromination took place in chloroform or acetic acid. Products obtained were the 4-bromo derivatives of 5-amino- (90%), 5-hydroxy- (95%), and 5-methoxy-benzisothiazole (40%). Use of the bromine-sulfuric acid-silver sulfate system raised the yield of the last-named product to 87% [80JCR(S)197]. 7-Amino-4-chloro-1,2-benzisothiazole was brominated in the 6-position [71JCS(C)3994].

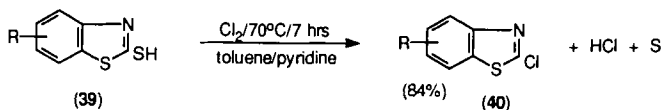
Chlorination of 1,2-benzisothiazole-3-one was found to give an *N*-chloro derivative (80MI2) in common with the result of treating the corresponding *S*-oxide with *t*-butyl hypochlorite (78JOU798). The sodium derivative of saccharin similarly reacted with chlorine, bromine, or bromine monochloride to form *N*-halogeno derivatives [73AHC(15)233; 76S736].

b. *2,1-Benzisothiazoles*. Like their isomers, 2,1-benzisothiazoles halogenate most readily at the 5- and 7-positions. Excess bromine converted the parent compound into 4,5,7-tribromo-2,1-benzisothiazole [72AHC(14)43]. 3-Chloro-2,1-benzisothiazole can be prepared either from the corresponding diazonium salt (71AJC2405) or by reaction of phosphoryl chloride with the benzisothiazolone (73JHC413).

14. *Benzothiazoles*

The 2-position is largely unreactive toward electrophiles, but nucleophilic substitution occurs there with some facility, especially in acidic medium. The protonated species is about 20 times more reactive than the neutral molecule (70BSF2705). Exhaustive chlorination in the presence of antimony trichloride gave pentachlorobenzothiazole (64GEP1168911). Direct chlorination of the parent heterocycle with aluminium or ferric

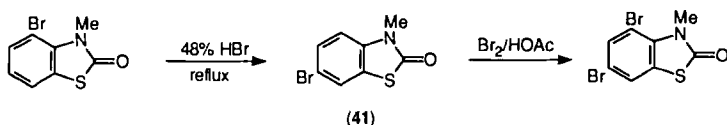
chloride catalyst, and with phosphorus trichloride or pyridine as co-catalyst, gave a 98% yield of 2-chlorobenzothiazole (40) (84GEP3234530). The 2-thiol (39) also formed 40 when heated with chlorine in the presence of a tertiary amine [86JAP(K)61/106563]. Heating at 160°C with phosphorus pentachloride also 2-chlorinated benzothiazole.



Attempts to brominate benzothiazoles with bromine in acetic acid at room temperature have given only perbromides, but when these were heated in ethanolic solution, products in which bromine had substituted in the benzene moiety were detected. At 100°C bromine in acetic acid gave rise to the 4,6-dibromo derivative in accord with calculated π -densities (70BSF2705). Vapor-phase bromination gave the 2-bromo product (84MI27).

When there is an electron-donating group in the homocyclic ring, bromination is directed *ortho* or *para* to that group, with some influence of the fused thiazole ring superimposed on these orientations (benzotriazole itself substitutes preferentially at the 4- and 6-positions). Thus, 4-amino-benzothiazole gave the 7-bromo product; the 5-amino isomer gave 4-bromo and 4,6-dibromo compounds; 6-aminobenzotriazole formed 5-bromo and 5,7-dibromo derivatives; 7-aminobenzothiazole gave 4-bromo and 4,5-dibromo products (65JCS2248).

When heated under reflux in 48% hydrobromic acid 4-bromo-2(3*H*)-benzothiazolones rearranged to the 6-bromo isomers (41). The mechanism is believed to involve initial protonation at C-4, followed by either bromide ion attack at C-6 (with concomitant S_N2' expulsion of the 4-bromine), or bromide attack at the 4-bromo group to remove it as molecular bromine. Subsequent electrophilic bromination at the 6-position is then possible. The latter process is favored by the authors. Further bromination of 41 gave a 32% yield of the 4,6-dibromobenzothiazolone (91T2255) (Scheme 26).



SCHEME 26

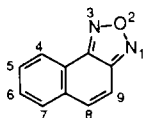
Most recent syntheses of fluorinated benzothiazoles make use of nucleophilic substitution. Potassium fluoride in acetonitrile converted **40** into the 2-fluoro derivative ($R = 6$ -nitro) in 99% yield. When the solvent was dimethylformamide the 2-dimethylamino derivative was formed instead [80JCS(P1)2358], and similar behavior was reported earlier (77BSF171).

15. *Benzisoselenazoles*

A mixture of mono-, di-, and tri-bromo compounds was formed on bromination of 1,2-benzisoselenazole. None of the five products had a bromine in the 3-position. Since nitration gave a 55 : 45 mixture of 5- and 7-nitro products, one might expect those to be the most reactive positions to bromination also (84MI32).

16. *Benzoxadiazoles*

Benzofurazan (benz-1,2,5-oxadiazole) reacted with bromine by addition to give a 4,5,6,7-tetrabromo adduct. Bromine in hydrobromic acid solution 4-brominated both 5-methyl- and 5-bromo-benzofurazans (74JHC813). When 4,7-dinitrobenzofurazan was treated with ammonium chloride in refluxing acetic acid, nucleophilic displacement gave rise to the 4-chloro-7-nitro derivative (83URP1004375). Naphtho[1,2-*c*]furazans (**42**) are mainly 4-halogenated, but there is minor substitution in the 8-position (73CHE1331).



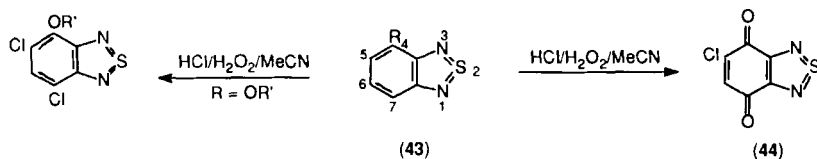
(42)

17. *Benzothiadiazoles*

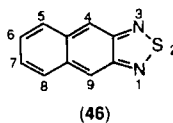
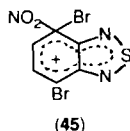
Benzo derivatives of 1,2,5-thiadiazole react readily with electrophiles; halogenation occurs in the homocyclic ring with an orientation similar to that of naphthalene. Benzothiadiazoles are, of course, much less reactive than naphthalene (84MI28). As with the analogous selenadiazoles, benzothiadiazoles undergo ready halogenation at the 4(7)-position. Deactivation of the 5(6)-position can be overcome by an electron-donating substituent at C-4, which makes it possible to prepare 5,7-dihalogenated derivatives.

An electron donor in the 5-position directs halogenation to carbon-4 (63JGU223, 63JGU1714).

In chlorinations either a substitution or an addition process can occur with the ultimate reaction pathway(s) determined by a combination of factors, which include the reaction conditions, the positions and natures of any substituents present, and the catalyst used. Uncatalyzed chlorination of benzothiadiazole is an exothermic reaction that gives rise to a mixture of isomeric tetrachloro addition products. These are converted in basic medium into 4,7-dichloro-2,1,3-benzothiadiazole (70RCR923). When an iron(III) catalyst is present 4- and 7-chloro substitution becomes the dominant process. Chlorination of a number of 4-substituted 2,1,3-benzothiadiazoles (**43**) using an oxidative process gave a combination of chlorinated and oxidized products. The 4-hydroxy, 4-amino-, 4-methylamino, and 4-acetoxy derivatives of **43** all formed the chloroquinones (**44**) (40–61% yields). With the 4-alkoxy substrates both **44** and some 5,7-dichlorinated product were obtained (88CHE96).



Bromination of **43** (R = H) also gave a tetrabromo product initially, but base treatment induced elimination with the formation of the 4,7-dibromo derivative (70RCR923), as well as about 20% of the 4,6- and a trace of the 4,5-isomers (70JHC629). With iron as catalyst, one molar proportion of bromine in a melt of **43** (R = H) resulted in almost exclusive formation of 4,7-dibromo-2,1,3-benzothiadiazole. Monosubstitution was not achieved under these conditions (70RCR923), but dropwise addition of a solution of bromine in 47% hydrobromic acid at 130°C gave the 4(7)-bromo compound (70JHC629). Bromine in acetic acid converted **43** (R = OH) into the 5,7-dibromo derivative (61M11). *Ipso*-substitution (chlorodenitration, bromo-, and chloro-desulfonation) is known at the 4-position (70RCR923). Some nitrations of bromobenzothiadiazoles exhibit transbromination as exemplified by the reaction of 70% refluxing nitric acid on the 4,7-dibromo derivative. Among the reaction products were the 4-bromo-7-nitro (67CHE662), 4,5,7-tribromo, and 4,5,6,7-tetrabromo derivatives (71JOC207). It is likely that the tri- and tetra-bromo derivatives were formed when the starting material was brominated by a Br⁺ species derived from an *ipso*-nitration intermediate (**45**).



Side-chain bromination occurred when 5,6-dimethyl-2,1,3-benzothiadiazole was treated with NBS (87CB1593). Both the 4- and the 4,7-dihalogenated compounds are readily made from the diazotized amino precursors (63JGU1714).

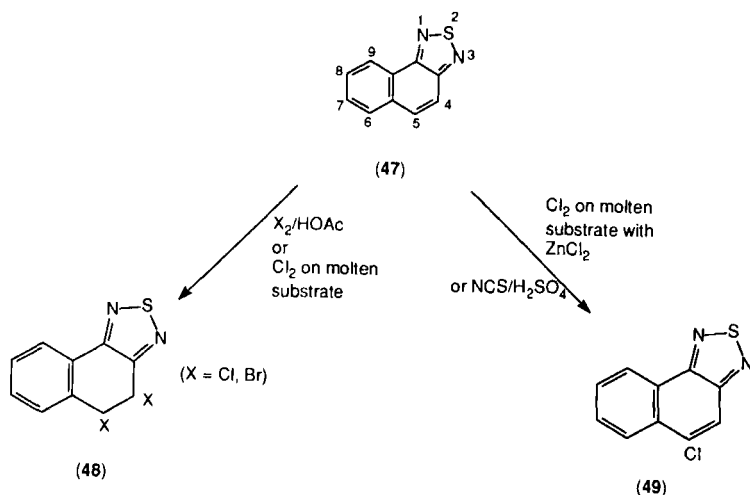
In the naphtho[2,3-*c*][2,1,3]thiadiazole (**46**) π -density calculations predicted an order for electrophilic substitution of $4 > 6 > 5$, in contrast to frontier electron density and localization energy predictions of $4 > 5 > 6$ [66TCA(5)401]. The transition state for 4-substitution is highly stabilized by carrying the positive charge on sulfur and having one fully benzenoid ring present. Despite of all this, bromination occurred at the 8-position initially (73CHE1331), and it was difficult to prevent polybromination (72ZVK348). Isomer distribution would be modified by N-protonation in acidic media. In the naphtho[1,2-*c*]isomer (**47**) the halogenation behavior resembles that of phenanthrene with most attack at the 4- and 5-positions, but with addition products predominating. Bromine in acetic acid gave the 4,5-dibromo-4,5-dihydro product (**48**; X = Br), and chlorine in acetic acid or with the molten substrate gave the analogue (**48**; X = Cl). The addition of chlorine in the presence of zinc chloride (or NCS in sulfuric acid) to molten **47** formed 5-chloronaphtho[1,2-*c*][2,1,3]thiadiazole (**49**), an apparent electrophilic substitution product, which may though be the consequence of an addition–elimination process (91JHC813) (Scheme 27).

18. Benzoselenadiazoles

5,6-Dimethyl-2,1,3-benzoselenadiazole was brominated on the methyl groups by NBS (87CB1593), but halogenation of the unsubstituted compound occurred, as with the sulfur analogue, at the 4(7)-position initially. Polybromination can occur (64JGU3063).

B. COMPOUNDS WITH TWO FUSED FIVE-MEMBERED RINGS

In this section coverage follows the general order of Part I [93AHC (57)271] in that heterocycles fused to furan will precede those fused to thiophene and pyrrole; fused oxazoles will precede fused thiazoles, etc.

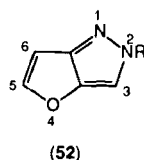
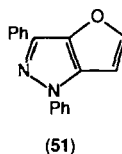
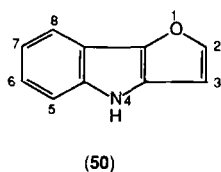


SCHEME 27

Some general information on halogenation of compounds that come under this heading has appeared recently [84MI20, 84MI30, 84MI31; 90AHC(47)181].

1. Furan Fused to Another Five-Membered Heterocycle

Bromination of 4H-furo[3,2-*b*]indole (**50**) occurred at the 2-position and was assisted by prior N-benylation; with the 4-benzoyl compound a 61% yield of the 2-bromo derivative was obtained. Thus, α -attack in the furan moiety predominates (78JHC123). When the pyrazolofuran (**51**) was treated with one molar equivalent of bromine, a mixture of the 2-bromo

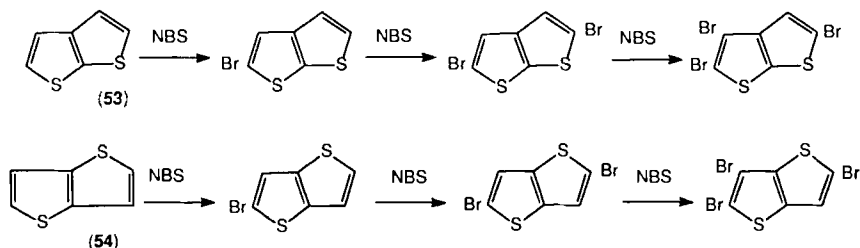


and *p*-bromophenyl derivatives was formed. With excess brominating agent both positions were substituted (78YZ204). With 5-methyl-1,3-diphenylfuro[3,2-*c*]pyrazole, however, the bromomethyl derivative was formed (78YZ264). When 2-substituted-2*H*-furo[2,3-*c*]pyrazoles (**52**) were brominated the order of bromine introduction was found to be $6 > 3 > 5$ (77MI1).

2. Thiophene (or Selenophene) Fused to Another Five-Membered Heterocycle

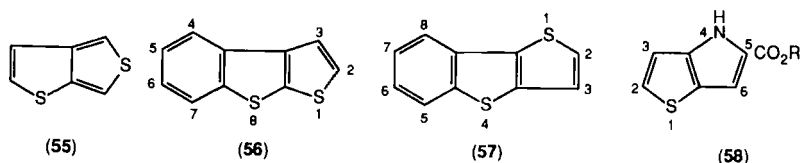
The bromination behavior of isomeric thienothiophenes (**53**–**55**) has been studied in detail. Both the [2,3-*b*] (**53**) and the [3,2-*b*] (**54**) isomers reacted with one equivalent of NBS in acetic acid to give an α -monobrominated product, with some evidence of 2,5-dibromo species also being formed. With 2 mol of NBS these latter products were formed in good yield; three molar equivalents led to 2,3,5-tribromothieno-[2,3-*b*]- and -[3,2-*b*]-thiophenes (Scheme 28). The monobromo compounds can also be prepared from lithium derivatives quenched with bromine [76AHC(19)123]. Apparently the [2,3-*c*] isomer (**55**) also reacted initially in the 2-position.

Chlorination of **53** and **54** with NCS occurred more rapidly than with thiophene itself [72CS(2)137]. Sulfuryl chloride treatment in carbon tetrachloride at -5°C gave the 2,5-dichloro derivative of **53**, but when only one molar equivalent of NCS was used there was a mixture of products including unchanged substrate (11%) and the 2-chloro (78%) and 2,5-dichloro (10%) derivatives. With double the proportion of NCS the yield of dichloro product was raised to 70%. Likewise, the isomer (**54**) gave mixtures of 2- and 2,5-dichloro products with no sign of any β -chlorination [76AHC(19)123; 80CS(15)206]. In the presence of mercuric oxide, iodine gave rather unstable 2-iodo derivatives of **53** and **54**, along with some unidentified diiodinated species [76AHC(19)123].



SCHEME 28

The predicted initial 2-substitution in thieno[2,3-*b*][1]benzothiophene (**56**) and the [3,2-*b*] isomer (**57**) was found to be true for bromination. Bromine in chloroform converted **57** into its 2-bromo derivative in 75% yield; further bromination gave a dibromo product of uncertain regiochemistry (thought to be the 2,6-dibromo compound). 3-Methylthieno[2,3-*b*][1]benzothiophene gave the 2-bromo derivative in 86% yield; because of the high bond order, the 2-methyl isomer similarly formed the 3-bromo product in 85% yield. Both the 3- and the 2-methyl-[3,2-*b*] compounds behaved similarly, but when the 2- and 3-positions were blocked by methyl groups, lateral methyl bromination took place before eventual 6-bromination [71JCS(C)463, 71JCS(C)1308].



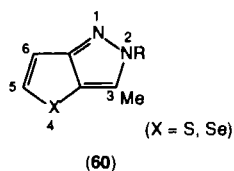
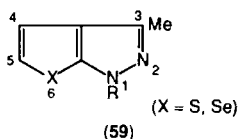
Selenophene is known to be more reactive with electrophiles than thiophene (see Part I;III,A,4), and so it is no surprise to find that in a quantitative study of the chlorination of thieno[3,2-*b*]thiophene, seleno[3,2-*b*]thiophene, and seleno[3,2-*b*]selenophene the 2-substitution rates relative to thiophene were 33 : 139 : 147 [80CS(15)206]. With 1 mol of NBS in acetic acid seleno[3,2-*b*]thiophene gave the 2,5-dibromo product (15–20%) and about 70% of the 5-bromo derivative (bromination in the α -position of the selenophene ring). Two equivalents of NBS gave 90% of the dibromo species. Similar results were obtained using bromine in chloroform, but excess bromine led to formation of a tetrabrominated heterocycle (70%) (80BAU286). When seleno[2,3-*b*]thiophene was treated with two molar equivalents of NBS the 2,5-dibromo derivative was formed, but one equivalent of the reagent produced a mixture of 4-bromo (80%) and 2-bromo (10%) products. The intermediacy of a Se-Br species has been suggested (72CHE424, 72CHE655, 80BAU286) as in dibenzoselenophene (39CB582, 39CB597) and in benzo[*b*]selenophene (74BSF2239). Quantum mechanical calculations on these sulfur and selenium heterocycles have been compared with the experimental bromination data, which demonstrated a high specificity (87–100%) for α -bromination in the selenophene ring (80CHE142).

Bromination also occurred in the 2-positions of seleno[2,3-*b*][1]benzothiophene and its [3,2-*b*] isomer (76MI1).

Thieno[3,2-*b*]pyrroles (**58**) reacted with bromine at both the pyrrole β -position and the thiophene α -position with comparable ease. No monosub-

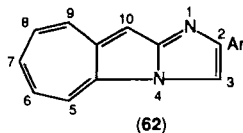
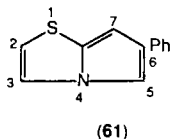
stituted products could be detected, and the deactivating substituent in the 5-position had little apparent effect on reactivity at C-6 [64JOC2160; 77HC(30)1; 78AHC(22)183]. Use of bromine in carbon disulfide in the presence of aluminium chloride catalyst resulted in the formation of an 84% yield of ethyl 2-bromothieno[3,2-*b*]pyrrolyl-5-carboxylate, demonstrating with this reagent a specificity for α -bromination in thiophene. Perhaps the Lewis acid complexes with the ester function to reduce reactivity at the adjacent site (84JHC215). Bromine in chloroform converted the *N*-methyl derivative of benzo[*b*]thieno[3,2-*b*]pyrrole into its 3-bromo derivative [73JCS(P1)125].

The 5-position was the most reactive in bromination of 1,3-disubstituted 1*H*-thieno- and -seleno-[3,2-*d*]pyrazoles (**59**), whereas the isomeric 2*H*-[3,2-*c*] derivatives (**60**) reacted at the 6-position [73JOU2216; 77CS(12)1].



3. Pyrrole Fused to Another Five-Membered Heterocycle

Bromination of 6-phenylpyrrolo[2,1-*b*]thiazole (**61**) occurred in the 5-position [77HC(30)1]. 1*H*-Pyrrolo[1,2-*a*]imidazoles reacted initially at the 5- and then at the 7-position [86HC(46)1]. 2-Arylcyclohepta[4,5]pyrrolo[1,2-*a*]imidazoles (**62**) were halogenated in moderate yield at both the 3- and the 10-positions, the former being the more reactive, as predicted by HOMO considerations. Reagents used were NCS or NBS in nonpolar solvents, bromine, and sulfuryl chloride in the presence of silica [84JCR(S)390].



4. Pyrazole Fused to Another Five-Membered Heterocycle

Most references involve studies of pyrazoloimidazoles. Bromine entered 1*H*-imidazo[1,2-*b*]pyrazole at the 7-position (equivalent to the 4-position in pyrazole) (78M11). Similar regiochemistry was observed when

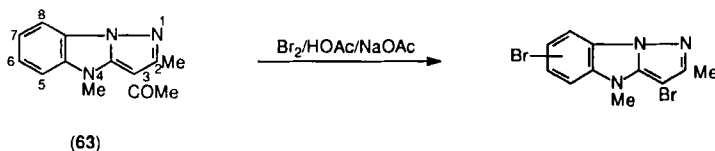
bromine in acetic acid converted 4*H*-pyrazolo[1,5-*a*]benzimidazole into its 3-bromo derivative (83M425). Indeed such a regiochemistry is quite general for pyrazoles fused to other heterocycles [78AHC(22)183]. When the 3-position was blocked as in 3-acetyl-2,4-dimethyl-4*H*-pyrazolo[1,5-*a*]benzimidazole (**63**) bromine in acetic acid containing sodium acetate gave a 33% yield of the 3,6(7)-dibromo derivative. With two equivalents of bromine the yield increased to 80% (Scheme 29). It is conceivable that the active reagent is acetyl hypobromite, which is able to achieve bromo deacetylation. When 1 mol of NBS in chloroform, carbon tetrachloride, or acetic acid at 25°C was used, only the 3-bromo product was observed, but two equivalents of NBS at 80°C gave the dibromo product. Chlorination experiments using 1-chlorobenzotriazole gave similar results (88CHE36).

Pyrazolo[1,2-*a*]pyrazoles give 3-bromo products unless the 3-position is blocked by a methyl when bromomethyl products arise (80JA4983; 81JOC1666, 87JOC1673). When all of the pyrazole ring positions are filled by phenyl groups, chlorination and bromination occur in the *para*-positions (74BCJ946) (see also B,1,2).

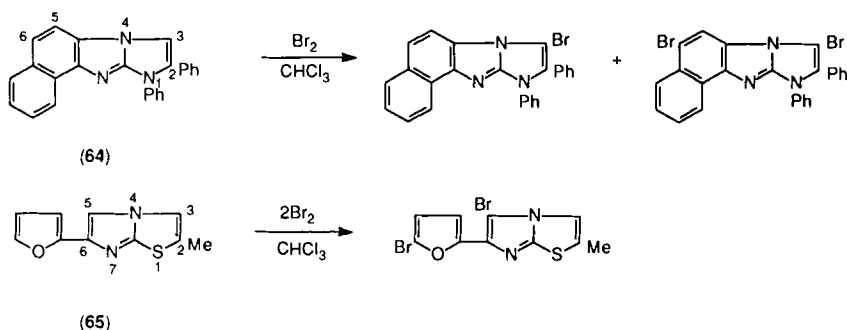
5. Imidazole Fused to Another Five-Membered Heterocycle

Bromination of 1*H*-imidazo[1,2-*a*]imidazole occurred at the 5-position (73JOC1955) (see also B,3,4). When 1,2-diphenylimidazo[1,2-*a*]benzimidazole was similarly treated with bromine in chloroform, the mixture of mono- and di-brominated products was assumed to include species with bromine at the free imidazole ring position, and *meta* in the 2-phenyl group (81CHE937). In the analogous naphthimidazoimidazole (**64**), bromination occurred at C-3 and C-6, and not at all in the phenyl substituents (82JOU193) (Scheme 30).

Treatment of 6-(2'-furanyl)imidazo[2,1-*b*]thiazole (**65**) with bromine in chloroform gave rise to products of bromination of both furan and imidazole moieties (80MI1). In the unsubstituted imidazothiazole, bromination in dimethylformamide at 80°C, or in dichloromethane at 0°C, occurred in the 5-position. Even when there are such reactive groups as 2'-furanyl or



SCHEME 29



SCHEME 30

2'-thienyl at C-6, bromine may enter the imidazole 5-position preferentially [72CHE1223; 86HC(46)1]. However, in 6-(2'-furyl)-3-methylimidazo[2,1-*b*]thiazole the first bromine entered the furan ring (75CHE45). Yields are usually high; e.g., the 6-methyl derivative gave an 88% yield of 5-bromo-6-methylimidazo[2,1-*b*]thiazole [91JCS(P1)855]. There have been other recent examples (91CCC2430).

Bromine in acetic acid attacked 2,5-disubstituted imidazo[1,2-*b*] [1,2,4]triazoles in the 6-position (70CB3533). There have been other examples in which high yields of brominated products were obtained (essentially C-5 of the imidazole nucleus is substituted) (85UKZ431). The same preference for imidazole substitution was observed in the bromination of 3-methylimidazo[1,2-*d*][1,2,4]thiadiazole (77G1), and in imidazo[2,1-*b*] [1,3,4]thiadiazole (83JHC1003).

6. Thiazole Fused to Another Five-Membered Heterocycle

Thiazolo[3,2-*b*][1,2,4]triazoles are often sufficiently reactive to be brominated in the thiazole nucleus (see also B,5). Thus, although the unsubstituted substrate and the 2-phenyl and 2-methyl derivatives would not react with NBS in refluxing chloroform, the 5-methyl, 2,5-dimethyl, and 5-methyl-2-phenyl compounds gave 6-bromo products (71JAP71/26498; 74JHC459).

7. Triazoles Fused to Another Five-Membered Heterocycle

Both rings were brominated when [1,2,3]triazolo[1,2-*b*][1,2,3]triazoles were treated with bromine in acetic acid (63CB1827) (see also B,5,6). The dibenzo derivatives brominated preferentially *para* to the nonfused nitrogens (67JA2626).

C. BENZO DERIVATIVES OF SIX-MEMBERED HETEROCYCLES

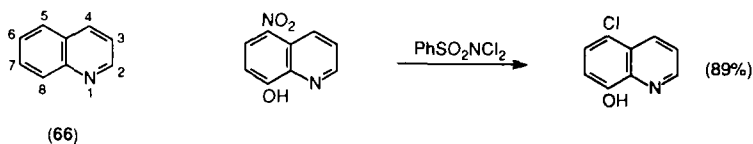
1. *Benzopyridines*

Halogenations of quinoline, isoquinoline, acridine, and phenanthridine will be discussed here. Reaction usually occurs in a homocyclic fused ring rather than in the π -deficient pyridine moiety, especially in acidic media. Relatively mild conditions suffice, but under more vigorous regimes radical involvement can result in heteroring halogenation. Substituents are able to modify reactivity and regiochemistry.

a. *Quinolines*. Few, if any, of the mono-, di-, and tri-halogenoquinolines are unknown. Earlier review material that has discussed aspects of the halogenation has been published [57CRV535; 66AHC(7)1; 74MI2; 77HC(32-1)319; 84MI2, 84MI3; 90AHC(47)303; 91MI6].

Chlorination. Electrophilic chlorination of quinoline (**66**) in neutral medium showed a positional selectivity order of $3 > 6 > 8$. The 5- and 8-positions should be sterically hindered to some extent. Hammett σ^+ values predict an order for electrophilic substitution of $5 > 8 = 6 > 3$. Treatment with chlorine at 160–190°C converted quinoline into a mixture of 3-chloro-, 3,4-dichloro-, 3,4,6- and 3,4,8-trichloro-, 3,4,6,8-tetrachloro-, and 3,4,6,7,8-pentachloro-quinolines. At lower temperatures ($\sim 100^\circ\text{C}$) the major product was 3-chloroquinoline, albeit in low yield. The 4-substituted species may have arisen from an addition–elimination or radical process [70JHC171].

In acidic medium ($\text{H}_2\text{SO}_4\text{--Ag}_2\text{SO}_4$) quinoline was converted into a mixture of 5- (17%) and 8-chloro (21%) and 5,8-dichloro-quinoline (32%) [63CI(L)1840; 66MI1; 81H(15)1285]. The 8-position appears to be the preferred site under these conditions [81JCS(P1)1520]. The general rule that seems to apply is that in neutral or weakly acidic media 3-chlorination is preferred; in strong acid 5- and 8-chlorination dominate. The suggestion has been made that N-chlorination (perhaps a complex) may be involved and that radical species become important at higher temperatures [77HC(32-1)319]. Prolonged treatment of **66** with chlorine–sulfuric acid–silver sulfate gave 3,8-dichloroquinoline, but no chlorination was observed when the acid concentration fell below 70% and in the absence of the silver salt. Nor were acetic, nitric, and hydrochloric acids effective media. The use of aluminium chloride under “swamping-catalyst” conditions gave a substrate resembling quinolinium (the catalyst fully complexes with the nitrogen), and chlorination occurred only in the fused benzene ring [77HC(32-1)319].



Polychlorination processes have included exhaustive chlorination in the presence of antimony pentachloride, which destroyed the molecule (1882JCS412). Chlorine in carbon tetrachloride gave 3,4,6,8-tetrachloroquinoline; chlorine dissolved in thionyl chloride gave the 4,5,7,8-isomer, whereas thionyl chloride alone produced a mixture of 3,4,5,6,7,8-hexachloro- (57%) and 3,4,6,8-tetrachloro- (37%) quinolines (73YZ73; 74S356, 74URP432143).

Substituent effects are largely as expected. An electron-withdrawing group in the benzene ring directs chlorination into the pyridine ring. Thus, sulfonyl chloride in *o*-dichlorobenzene or NCS in acetic acid converted 8-nitroquinoline into the 3-chloro derivative in high yields (84, 96%) (91M935). Activating groups direct chlorination *ortho* and *para* to themselves, even when electron-attracting groups are also present. Chlorine in acetic acid 5,7-dichlorinated 8-amino-, 8-methoxy-, and 8-hydroxy-quinolines [72JOC4078; 77HC(32-1)319], and 8-amino-4,7-dichloroquinoline was further chlorinated in the 5-position. 6-Methoxy-8-nitroquinoline gave the 5-chloro derivative (72JOC4078). Reaction of 2-chloro-6-methoxyquinoline-3-aldehyde and its 7-methoxy analogue with chlorine in 1,2,4-trichlorobenzene (or with sulfonyl chloride) gave the 2,5- and 2,8-dichloro products, respectively, in 70–80% yields (91SC1929). All of the possible monochloro 8-quinolinols have been prepared (91M935).

In basic medium 8-hydroxyquinoline reacted as the anion to form the 7-chloro product. Treatment of 8-methylquinoline with chlorine–sulfuric acid–silver sulfate gave a high yield of the 5-chloro derivative (83CHE1093). In contrast to the halogenation of 4-hydroxyisoquinoline (Section C,1,c), 3-hydroxyquinoline gave the 4-chloro product with no dichlorination with excess reagent (71BAU400). 2-Quinolone, however, was 3,6-dichlorinated (72JOC4078). Activation by both an *N*-oxide group and a 3-hydroxy function renders 4-chlorination by concentrated hydrochloric acid and hydrogen peroxide a facile process (84BAU1522).

Oxidative chlorination of 1,10-penanthroline using excess phosphorus pentachloride and phosphoryl chloride gave rise to high yields of products chlorinated *meta* and *para* to the annular nitrogens (92BCJ2007).

There are numerous examples of the conversion of hydroxyquinolines and quinolones into the chloro derivatives using phosphoryl chloride and

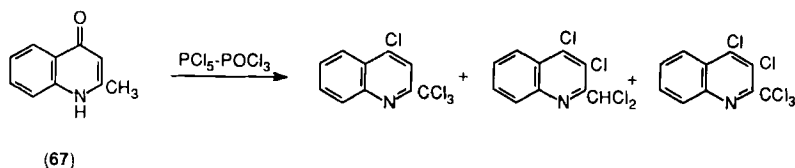
other standard reagents to displace the oxy function [72JOC4078; 77HC(32-1)319; 81CPB1069; 86M1305; 91M935, 91MIP1]. Three recent examples were the transformations of 8-acetoxy-2-hydroxy- and 4-hydroxy-8-methoxy-quinolines into the 2- (77%) and 4- (78%) chloro derivatives (91M935) and the synthesis of 4-chloro-3-nitro-2-quinolone in 92% yield from the 4-hydroxy precursor (92JHC225). These processes are especially indicated when 2- and 4-chloroquinolines are required.

Other nucleophilic substitution reactions leading to chloroquinolines have included replacement of a 5-nitro group by the use of aryldichlorosulfonamides in reactions that were accompanied by some 7-chlorination (83MI2) (see p. 287). Halogen-halogen exchange processes [69CI(L)943] and reactions of chloride with diazonium salts have also been employed frequently. Diazo groups at C-2 and C-4 are so reactive that they can be displaced by chloride even without the need for a copper catalyst [77HC(32-1)319].

In the Meisenheimer reaction of quinoline 1-oxides chlorine atoms usually enter the 2- and 4-positions, but not exclusively. 2,4-Dibromoquinoline 1-oxide was 6-chlorinated (57MI1), and the 5- and 6-nitroquinoline 1-oxides were 3-chlorinated to some extent (44JOC302). This reaction with phosphoryl chloride-phosphorus pentachloride has also been used in the preparation of chlorinated phenanthrolines (88YZ1148).

Sometimes lateral chlorination can occur on a methyl or alkylthio substituent, especially when phosphorus pentachloride or its mixtures with phosphoryl chloride are used (91JHC1549). Reactions of 2-methyl-4(1*H*)-quinoline (67) exemplify this behavior (81CPB1069) (Scheme 31); 2-chloro-3- and -4-methyquinolines are also subject to methyl chlorinations by similar reagents (91JHC1549). Sulfuryl chloride and NCS are also likely to induce a proportion of lateral chlorination (83KFZ1055; 86S835).

Bromination. Neutral bromination of quinoline (66) using bromine in hot carbon tetrachloride and pyridine gave the 3-bromo derivative (68) (90%) and 3,6-dibromoquinoline (69) (2%), along with traces of 3,8-di- and 3,6,8-tri-bromo products [59CI(L)1449; 66AHC(7)1]. There is some

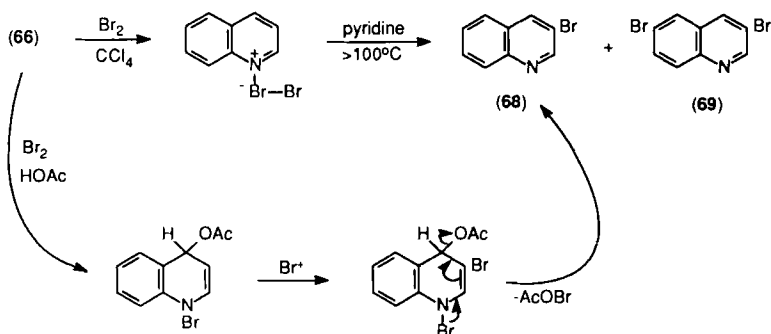


SCHEME 31

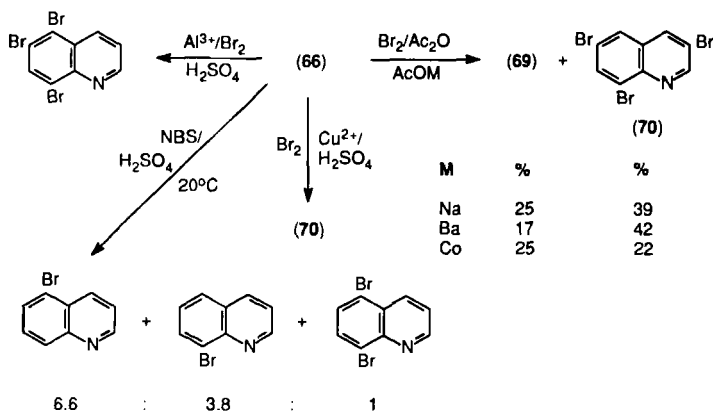
evidence that an addition–elimination mechanism is operating in neutral bromination [62JCS291; 90AHC(47)385] (Scheme 32). Certainly it is polar rather than radical. The heterocycle appears to form a quinoline–bromine complex below 100°C with the ultimate product (**68**) being formed in the presence of pyridine. The complex, believed to be an n -donor complex, can be prepared in dry carbon tetrachloride. It decomposes on boiling to give a mixture of **68** and quinolinium perbromide. Pyridine promotes the ready elimination of HBr [62JOC1318; 63JOC2865] (Scheme 32).

With acetic acid as solvent **68** is still the major product (Scheme 32). The minor product (**69**) probably forms in preference to the 3,5-isomer because the quinoline free base is reacting; the high yield of **68** can be rationalized in terms of a 1,4- or 1,2-addition product that is rapidly brominated at C-3. The 6- and 8-positions substitute more slowly [62JCS283, 62JCS291; 77HC(32-1)319]. Both the 6- and the 8-bromoquinolines were 3-brominated under “neutral” conditions (62JOC1318).

Bromination of the quinolinium species in strongly acidic media results in 5- and 8-bromo products. Bromine in oleum [02JPR(174)209], in sulfuric acid with silver sulfate [58CI(L)361; 60JCS561; 75JHC1015; 81H(15)1285], or in the presence of a Lewis acid catalyst (64JOC329; 85CHE458) produced varying mixtures of 5-bromo-, 5,6-, and 5,8-dibromo-, and 5,6,8-tribromoquinolines. The unexpected 3-bromination (81%) of quinolinium chloride in nitrobenzene has been rationalized by postulating the formation of a 1,2-dibromo complex that is brominated at the 3-position (73JHC409). A detailed study of the regiochemistry of quinoline bromination in the presence of a variety of Lewis acids has pointed to some marked differences. Catalysts derived from elements with p -orbitals (e.g., Al, In, Sn) and d -orbitals (e.g., Cu, Zn) were highly active and quite marked for the p -elements. It had been expected that the d -elements might direct the



SCHEME 32



SCHEME 33

orientation of bromination rather differently than is the case with silver sulfate since “ π -back-donation” is possible. Reaction in 94% sulfuric acid in the presence of Al^{3+} gave 5,6,8-tribromoquinoline with the pyridine ring highly deactivated. The anomalous formation of the isomer (70) in the presence of copper(II) sulfate was ascribed to a decrease in the positive nature of the quinolinium cation in strong acid because of back-donation from the Cu^{2+} d -orbitals (85CHE458) (Scheme 33). Treatment of 6-fluoro-2-methylquinoline with bromine and aluminium chloride in 1,2-dichloroethane gave a mixture of the 5-bromo (80%) and 5,8-dibromo (10%) products (92JHC895).

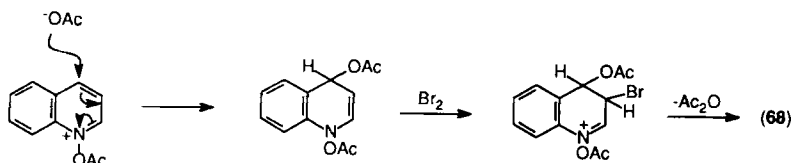
Reactions in acetic anhydride with metal acetates present probably occur by 1,4-addition of bromonium acetate (85CHE458). When NBS in sulfuric acid at 20°C was used, the product ratio resembled that observed with bromine-sulfuric acid-silver sulfate. At 60°C the ratio changed to 2:1.2:1 as a consequence of more extensive dibromination (88CHE892) (Scheme 33). As might have been deduced, 2-(2'-thienyl)quinoline was brominated only in the thiophene ring (82CHE28).

Bromine in acetic acid readily converted the activated 3-hydroxyquinoline into its 4-bromo derivative (76%); under similar conditions 8-hydroxyquinoline gave a mixture of the 5-bromo and 5,7-dibromo compounds [71BAU400; 72JOC4078]. All of the possible monobromo derivatives of the latter substrate have been made (91M935). 4-Hydroxy-1,3-dialkylquinolin-2(1*H*)-ones were brominated (and chlorinated) at the 3-position or at C-6 if the former was already substituted [86JCR(S)122; 90LA1083; 92M617]. Oxidative bromination, using sodium bromide and bromate in hydrochloric acid, converted 8-hydroxyquinoline into the 5,7-

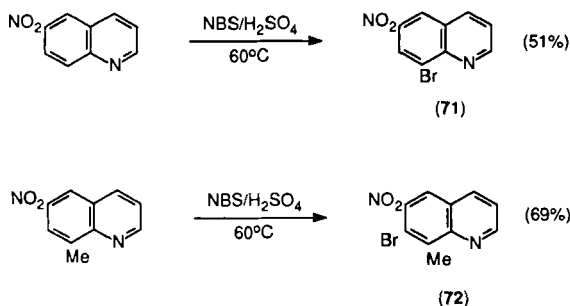
dibromo derivative in 90% yield. Bromoperoxidase and hydrogen peroxide gave a 79% yield (87JHC1313). 8-Methoxyquinoline was converted by NBS into the 5-bromo product, as was the 8-hydroxy analogue, but in basic medium 7-bromination was observed (72JOC4078). Bromine dissolved in 10% aqueous sodium hydroxide 4-brominated 3-hydroxyquinoline in 78% yield (71BAU400), and there are other examples of similar brominations *ortho* to a methoxy group (91SC1929). In the 6- and 8-methylquinolines the orienting effects of the ring and substituent coincide to direct specific 5-bromination. Yields of 74% ($\text{Br}_2\text{-H}_2\text{SO}_4$) and 58% ($\text{NBS-H}_2\text{SO}_4$) were obtained, and further attack occurred at the 8- and 7-positions, respectively. 7-Methylquinoline was brominated in both 5- and 8-positions (83CHE1093; 88CHE892), whereas 2-alkyl-6-bromoquinolines reacted with bromine-sulfuric acid-silver sulfate to give mainly 5-brominated material [81JAP(K)128762].

In acetic acid quinoline 1-oxide was converted into the deoxygenated 3-bromo derivative (**68**) and some 69 by a process outlined in Scheme 34 (61CPB414; 65YZ62). With bromine in aqueous solution (47JPJ87), or bromine in acetic acid in the presence of thallium acetate, the 4-bromo 1-oxide was formed almost certainly by an electrophilic process. The former conditions gave a yield of only 3–4% as against 60% with the thallium reagent. Similarly, the 2-methyl-, 2-cyano-, and 3-bromoquinoline 1-oxides formed 4-bromo products in yields of 22, 63, and 95% [79H(12)475]. Activation by both an *N*-oxide and a 3-hydroxyl group makes 4-halogenation even more facile with a variety of brominating agents (84BAU1522).

Electronegative groups do not invariably prevent nuclear bromination, but reaction conditions must be much more severe, and the orientation of substitution may be affected by the substituent. Thus 6-nitroquinoline was brominated in sulfuric acid at 100°C to give the 8-bromo product (**71**) in 51% yield; 8-methyl-5-nitroquinoline gave a 69% yield of the 7-bromo derivative (**72**) under similar conditions, whereas 7-chloroquinoline was transformed into the 5-bromo product (93%) (88CHE892) (Scheme 35). In a sealed tube reaction with bromine, 8-nitroquinoline gave a mixture



SCHEME 34



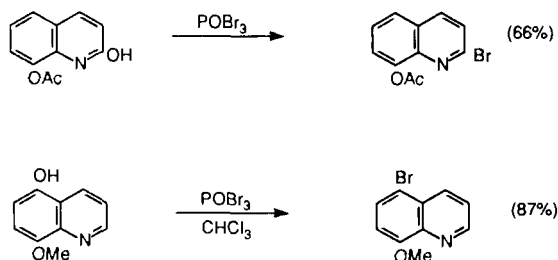
SCHEME 35

of 3-bromo and 3,6-dibromo products; similar treatment of the 6-nitro isomer led to the 3-bromo product, as did bromine in carbon tetrachloride and pyridine [77HC(32-1)319]. These products contrast with those formed from reactions in sulfuric acid where the quinolinium species is substituted only in the homocyclic ring.

Vapor phase brominations have given rise to varying products dependent on the reaction temperature. At 300°C bromine converted quinoline in the presence of pumice into **68** (25%); at 450°C 2-bromoquinoline (25%) became the major product; at 500°C the yield of the 2-bromo isomer increased to 53%, but there was some dibrominated material [77HC(32-1)319]. The absence of 3-bromoquinoline at the higher temperatures could be accounted for in terms of radical attack, or it could be due to thermal instability of that isomer [59CI(L)1449].

It is seldom easy to form polybromoquinolines in high yields. Most reagents give mainly monobromo products, although moderate yields of di- and tri-bromoquinolines become possible with Lewis acid catalysts, or by bromination in acetic anhydride in the presence of metal acetates (85CHE458) (Scheme 33). Recently, reaction of quinoline with bromine in thionyl chloride [as for 1,10-phenanthroline (78JPR172)] was reported to give **69** (60%), **70** (6.5%), 3,6,8-tribromo-4-chloroquinoline (7%), and 3,5,6,8-tetrabromoquinoline (8.2%) (91JPR351). Combinations of electrophilic and nucleophilic halogenations appear to offer the best chance of making polybromoquinolines.

Among the nucleophilic processes available for introduction of bromine to quinolines are reactions of the diazonium salts (87JHC181) and syntheses based on hydroxyquinolines or quinolones (91M935) (Scheme 36). The former processes are especially useful for making 5-, 6-, 7-, and 8-bromo derivatives. Halogen-halogen exchange reactions have also been reported, but they are not common. When perfluoroquinoline was heated



SCHEME 36

at 150°C with boron tribromide an 88% yield of 2,4-dibromoperfluoroquinoline was obtained [69CI(L)943].

Lateral bromination was observed in the reaction of NBS with 5-chloro-8-methyl- and some related methyl- and alkylthio-quinolines [83KFZ1055; 86S835].

Iodination. Direct iodination of quinoline in neutral medium gave only ill-defined products containing, perhaps, some 3-iodoquinoline [66MI2; 77HC(32-1)319]. The process is difficult, requiring temperatures around 150–200°C. Acidic conditions seem to be much more successful, except that the regiochemistry is different. In above 80% sulfuric acid containing iodine and silver sulfate, quinoline was converted into a mixture of 5- and 8-iodo and 5,8-diiodo-quinoline. No triiodination was observed, and the 8-position appeared to be the preferred site [64CI(L)1753; 66MI2; 81H(15)1285, 81JCS(P1)1520]. Iodination is a much slower reaction than chlorination or bromination and occurs best when there are activating substituents present (80CHE275). Thus, 8-methylquinoline readily formed the 5-iodo derivative in 90% yield at room temperature using the acidic reagent mixture (83CHE1093), whereas iodine in aqueous methanol converted 7-chloro-8-hydroxyquinoline into the 5-iodo derivative (98%) (71JHC821). Iodination of both 8-hydroxy- and 8-methoxy-quinolines with NIS in acidic or neutral conditions gave the 7-iodo derivatives (*cf.* chlorination and bromination). This site selectivity may be the result of steric hindrance at a *peri*-position. In basic medium, though, the anion of 8-hydroxyquinoline gave the 5-iodo product; 8-methoxyquinoline did not react under these conditions (72JOC4078). A hydroxyl group in the 3-position directed iodination into the 4-position (88%) with no diiodination observed (71BAU400). The same site selectivity was found when 3-hydroxyquinoline 1-oxide was treated with iodine and potassium iodide in 10% aqueous caustic soda (84BAU1522).

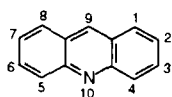
Halogen exchange with metallic derivatives provides a powerful means of introducing iodine into specific quinoline sites. It has proved possible to prepare 2-, 3-, and 4-iodoquinolines from the trimethylstannyl [82H(19)168] or lithium derivatives [86S670]. Protected 2-aminoquinoline, lithiated at C-3, was quenched with iodine to give a 90% yield of the 3-iodo derivative (86S670).

Sandmeyer reactions of diazonium salts are an obvious source of iodoquinolines [77HC(32-1)319], but other nucleophilic displacements are even more common. Heating 2-chloroquinoline with HI in the presence of red phosphorus, or with iodomethane in a sealed tube (this reaction involves attack by iodide on the quaternary salt), introduced an iodine at C-2 [1894LA(282)363; 77HC(32-1)319]. Cross-linked polystyrene 4-vinylpyridinium dichloroiodate smoothly converted 5-chloro-8-hydroxy-7-iodoquinoline into the 5,7-diiodo derivative (81%) [89JCS(P1)2279]. Reaction with sodium iodide in refluxing acetonitrile gave a 90% yield of 2-iodoquinoline-3-aldehyde from the chloro analogue [81JCS(P1)2509].

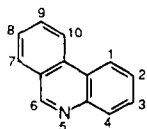
Fluorination. Direct fluorination of quinoline was accompanied by extensive fragmentation of the heteroring, but trifluoromethyl hypofluorite in trichlorofluoromethane at -70°C converted 5-fluoro-8-hydroxyquinoline into the 5,7-difluoro-8-hydroxy product (72JMC987). Quinoline, itself, was perfluorinated by fluorine and cobalt(III) fluoride (56JCS783), whereas cesium tetrafluorocobaltate at around 350°C converted it into a mixture of saturated polyfluoro compounds (82JFC413). It is much more satisfactory to introduce fluorine by nucleophilic methods.

5-Fluoro-8-methylquinoline was made from the diazonium salt by either thermal or photolytic methods (83CHE1093). With the possible exception of 4-fluoroquinoline, which appears to self-quaternize, all of the monofluoroquinolines are available from the amino precursors (49JA1785). Nucleophilic displacement of another halogen by fluoride is exemplified by the preparation of 2-fluoroquinoline in 60% yield from the 2-chloro compound using potassium fluoride in dimethyl sulfoxide (62RTC1058). Treatment of 2-chloroquinoline with tetrabutylphosphonium hydrogen difluoride (or dihydrogen trifluoride) under mild conditions gave 2-fluoroquinoline in 99% yield [92H(34)1507]. Chlorine-fluorine exchange at C-3 of some 3-chloroquinolin-2,4-diones has been reported (92M617). Hydroxy (using trifluoro-1,2,3-triazine) (60BRP845062) and nitro groups (87JHC181) have also been replaced by fluoride.

b. *Acridines and Phenanthridines.* Fusion of two benzene rings to pyridine can give acridine (73) or phenanthridine (74).

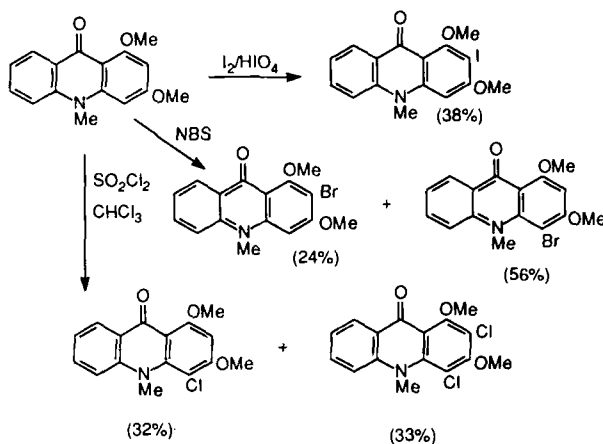


(73)



(74)

In acetic acid, acridine was brominated to give mainly the 2-bromo derivative and some 2,7-dibromoacridine (total yield 75%) (54JCS4142). Chlorination with thionyl chloride gave the 9-chloro derivative (83PHA83); acridine *N*-oxide was similarly brominated and chlorinated at the 9-position (60JCS3367). Electron-donating substituents direct attack into positions *ortho* and *para* to themselves. Thus, 1,3-dimethoxy-10-methyl-9-acridone was halogenated by a variety of reagents in the 2- and 4-positions. There was no attack in the other fused ring (84LA31) (Scheme 37).



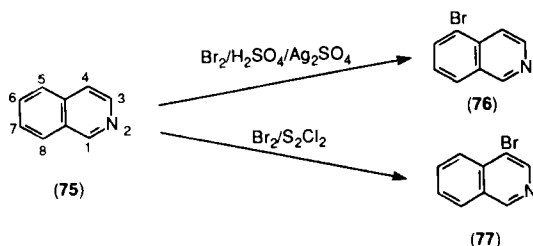
SCHEME 37

Phenanthridine (**74**) was converted by NBS into the 2-bromo derivative (40%) (55JA6379), but the bromine–sulfuric acid–silver sulfate reagent gave low yields of 1-, 4-, and 10-bromophenanthridines in the ratio (1 : 6.4 : 9.5), a reactivity order which contrasts with that found in nitration (1 > 10 > 4 > 2) (69AJC1105). Phosphoryl chloride converted phenanthridine 5-oxide into the 6-chloro derivative, but when that position was blocked by a phenyl substituent, the reductive chlorination process gave a 2-chloro compound (84MI2).

c. *Isoquinolines*. There have been few references to the halogenation of this system in recent years, but review material has appeared [84MI2; 90AHC(47)382]. The parent compound (**75**) resembles quinoline in its reactions with electrophiles. Halogenation in acidic medium usually occurs in the fused benzene ring. There are areas of uncertainty about the exact mechanism operating when the free base reacts, as with quinoline. Positional reactivity orders for the free base have been quoted as $5 > 8 > 7 > 6$ for isoquinolinium species, and the 4-position is the most reactive in the free base [90AHC(47)382].

Chlorination. When **75** was treated with chlorine in the presence of aluminium chloride, initial chlorination took place at the 5-position, but the reaction was rather unselective; 5,8-di-, 5,7,8-tri-, and 5,6,7,8-tetrachloroisoquinolines were also formed (64JOC329). Perchlorination has been achieved by initial reaction of the isoquinoline–aluminium chloride complex with chlorine, as above, followed by treatment with phosphorus pentachloride at 270°C in an autoclave [66JCS(C)2328]. Treatment of 1,8-dimethylisoquinoline with NCS gave the 5-chloro derivative (91NKK-1193). Meisenheimer reaction of isoquinoline 2-oxides with phosphoryl chloride gave 1-chloroisoquinoline (84MI2).

Bromination. With one equivalent of bromine the isoquinoline–aluminium chloride complex was converted into 5-bromoisoquinoline (**76**) (76%); two equivalents of bromine gave 5,8-dibromoisoquinoline (55%); 3 mol of bromine resulted in the formation of a mixture of 5,6,8- and 5,7,8-tribromo derivatives, with the 7-position being slightly more reactive than the 6-position (59MI1; 64JOC329). Bromination in strongly acid medium gave **76** initially (Scheme 38). When the free base form reacts, as with sulfur monochloride in thionyl chloride, the 4-bromo isomer (**77**) is formed preferentially (60JA4430). The same product was formed in 76% yield when **75** hydrochloride was treated with bromine in nitrobenzene (73JHC409). This regiochemistry must be a consequence of the more reactive free base being involved. Bromination in the presence of silver sulfate gave a mixture of 5-bromo and 5,7-dibromo derivatives of 1,8-



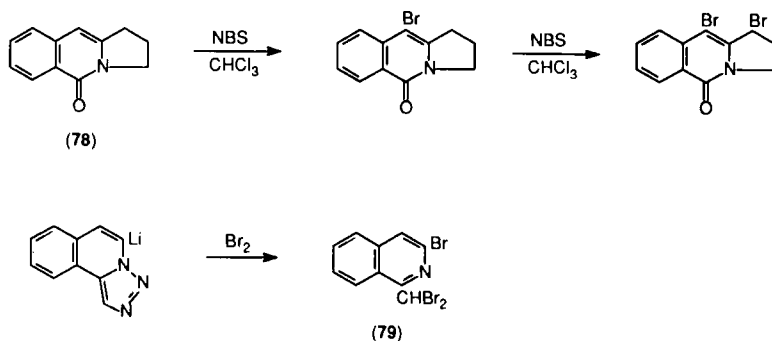
SCHEME 38

dimethylisoquinoline (91NKK1193). When the 5-position is blocked bromination of the cationic species usually occurs at the 8-position.

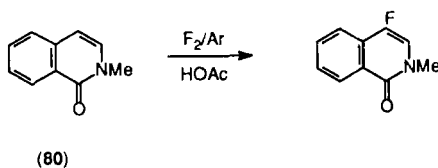
Activating groups greatly enhance reactivity and direct the incoming electrophile into positions *ortho* and *para* to the substituent. 4-Hydroxyisoquinoline gave 3-bromo (76%) and 1,3-bromo (40%) derivatives when treated with 1 and 2 mol of bromine (71BAU395; 71BAU400). When NBS is used an alkyl substituent may be brominated; bromomethyl products were isolated when 1,8-dimethylisoquinoline was so treated (88M11), whereas the isoquinolone (78) gave products of both annular and lateral bromination (83CPB2275) (Scheme 39).

Isoquinoline 2-oxide was converted by bromine in acetic anhydride in the presence of sodium acetate into the 4-bromo 2-oxide, presumably via an addition-elimination process (84MI2). Metallic derivatives have been used occasionally to prepare bromoisoquinolines, as in the formation of 79, a process accompanied by ring-opening [87JCS(P1)1865].

Iodination. Direct iodination is common only with activated isoquinolines. Treatment of 4-hydroxyisoquinoline with 1 mol of iodine with potassium iodide in aqueous sodium hydroxide gave the 3-iodo prod-



SCHEME 39



SCHEME 40

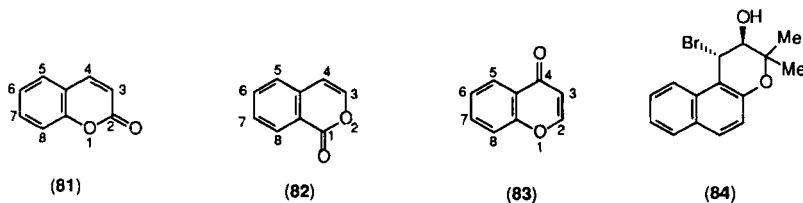
uct in 88% yield. With two equivalents of iodine a 50% yield of the 1,3-diiodo derivative was isolated (71BAU395; 71BAU400). 5-Iodo-1,8-dimethylisoquinoline was made in analogous fashion to the bromo compound (91NKK1193). Equal proportions of iodine in chloroform or tetrahydrofuran converted 1-, 3-, and 4-trimethylstannylisoquinolines into the corresponding iodo derivatives [82H(19)168].

Sandmeyer reactions used have included the preparation of the 5-iodo compound from the diazonium salt of 5-amino-8-isoquinolinol; further reaction with iodine monochloride gave 5,7-diiodo-8-isoquinolinol (66JMC46). Treatment of 1-chloroisoquinoline with iodide gave the 1-iodo analogue (47%) (67YZ1342).

Fluorination. Attention has been focused on the direct fluorination of isoquinolines activated by conversion into 2-methylisocarbostyryl (80). With gaseous fluorine (diluted to 10% with argon) in acetic acid a 54% yield of the 4-fluoro derivative was obtained. (Scheme 40). With methylene chloride as the solvent, only the 4-chloro analogue was formed [82H(17)429]. Fluoroisoquinolines have also been made by displacement of nitro groups, and from diazonium fluoroborates (87JHC181). Heptachloroisoquinoline was converted into a perfluoro derivative by heating it in an autoclave with anhydrous potassium fluoride [66JCS(C)2328].

2. Benz Derivatives of Pyrans, Pyrones, and Their Sulfur Analogues

Whereas benzopyrylium salts are resistant to electrophilic substitution, even in the benzene moiety, the benzopyrones [coumarins (81), isocoumarins (82), and chromones (83)] are readily halogenated in either ring, with

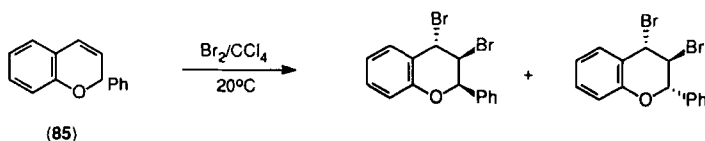


substituents frequently exerting the dominating effect on regiochemistry. As with the monocyclic species, halogenations are commonly of the addition-elimination type [84MI12, 84MI13; 90AHC(47)353].

a. *Benzopyrans*. At room temperature or below, chlorine and bromine converted 2*H*-chromenes into 3,4-dihalides, although 7-methoxy functions hindered the reactions [66JCS(C)2013]. Sometimes spontaneous dehydrobromination gave 3-bromo-2*H*-chromene as product. Both 2,2-dimethyl-2*H*-chromene and the corresponding naphth[2,1-*b*]pyran reacted with hypobromous acid to give 4-bromo addition products (e.g., **84**) (60JCS3094). At room temperature 3-chromene (2*H*-flavene) (**85**) added bromine to form the *trans*-dibromo products in 50% yield (67T341) (Scheme 41). A recent review of 3-chromene chemistry contained no halogenation data (91BSF189). A 65% yield of the 3,4-dibromo product was obtained on treatment of 2,2-dimethyl-7,8-diacetoxychroman with NBS in the presence of benzoyl peroxide (92MI1).

b. *Benzopyrones*. Coumarins (**81**) add halogens across the 3,4-bond; subsequent dehydrohalogenation gives 3-halogeno products. The presence of a hydroxyl group in the 4-position did not prevent 3-bromination (73JOU2160). Recently 4-fluorocoumarins were made by halogen exchange from the 4-chloro analogues, using potassium fluoride in the presence of 1-methylpyrrolidone. Yields were in the range 44–80% with a number of 3- and 6-substituents (H, Me, Cl, F) (91S937). Such nucleophilic substitutions are favored at the 4-position.

A variety of halogenating agents (Br₂, Cl₂, I₂, NCS, NBS, CuCl₂, CuBr₂, chloranil, bromanil) have been used to convert 7-aminocoumarins into their 3-halogeno derivatives. Solvents used were acetonitrile, dioxan, nitromethane, pyridine, dichloromethane, chloroform, acetic acid, and 50% aqueous sulfuric acid; yields were high with all reagents, but the best were found to be NBS in acetonitrile (80–94%), NCS and CuCl₂ (70–95%), and iodine–dioxan–pyridine (70–95%). Additional chlorination at C-8 occurred when NCS was used (90CHE1329). Iodine monochloride gave the 5-iodo derivative of 6-aminochromone (92MPI1). Radioiodination of 7-methoxy- and 6,7-dimethoxy-4-bromomethylcoumarins gave 3-(¹²⁵I)iodo

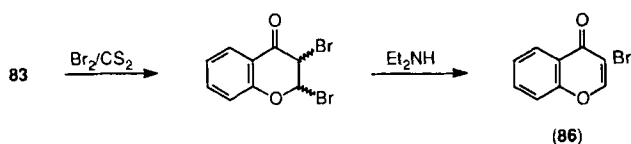


SCHEME 41

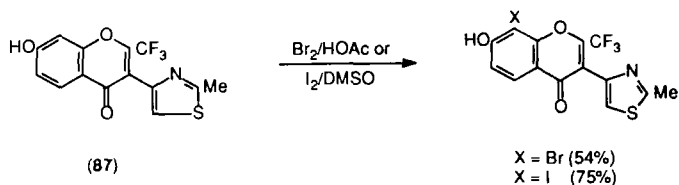
derivatives (91MI4). 3-Acetyl-5,6-benzocoumarin was brominated on the exocyclic methyl function (92ZOB661).

3-Chloroisocoumarin reacted by addition with chlorine to give a high yield of 3,3,4-trichloro-3,4-dihydroisocoumarin (73JOU2160).

Chromone (**83**) also reacts by initial addition; in the presence of a suitable base the 3-bromochromone (**86**) is formed (Scheme 42). Whereas the pyran ring in chromones (and flavones) is not particularly susceptible to electrophilic attack, electron donors at C-2 or C-3 can activate the adjacent ring position. The 2-carbamate ester of **83** brominated readily at the 3-position (73KFZ9) and 3-hydroxychromone gave the 2-bromo product even though the 2-position is not commonly subject to electrophilic attack [75AP385; 78JCR(S)47]. Reaction with NBS is aqueous dimethyl sulfoxide added HOBr across the 2,3-bond of chromone and a series of 3-substituted chromones (75JHC981). Flavone (2-phenylchromone) at first formed a 2,3,3-trichloro derivative when treated with sulfonyl chloride, but subsequent catalytic hydrogenolysis in the presence of base converted it into 3-chloroflavone (70CC380). Chromone, itself, behaved similarly when it formed the 2,3-dichloro-2,3-dihydro derivative (67CHE624). The hydrogen bromide or chloride formed when addition products dehydrohalogenate can protonate the pyran and deactivate it. Furthermore the fused benzene ring is deactivated by the carbonyl group, rendering halogenation difficult in the absence of activating groups. It was possible to 8-brominate and -iodinate 3-(4'-thioazolo)-7-hydroxychromones (**87**) (Scheme 43). Ultimately, the use of excess bromine led to the 5,8-dibromo derivative (82CHE240). 7-Hydroxy-2-methylchromone and a number of hydroxyflavones behaved similarly [70JCS(C)2230; 78CHE497]. The parent compound (**83**) was brominated at room temperature by dibromoisocyanuric acid, a reagent capable of introducing up to four bromine atoms into the chromone system, depending on the relative molar ratios of reagent to substrate. In sulfuric acid the reagent is a potent source of electrophilic bromine. The products isolated included 6-bromochromone and the 5,6,8-tribromo and 3,5,6,8-tetrabromo derivatives. Even 6-nitrochromone was converted by this reagent into the 3,8-dibrominated product [73JCS-(P1)2781].

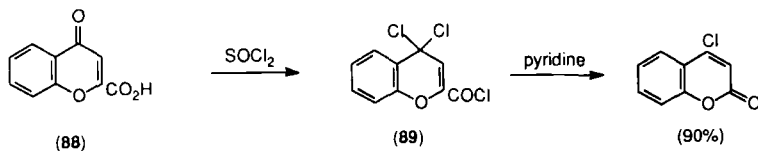


SCHEME 42



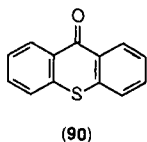
SCHEME 43

Flavones, lithiated at the 3-position with LDA gave high yields of 3-iodo derivatives when quenched at -78°C with iodine in tetrahydrofuran [85JCS(P1)799]. Although neither pyrones nor thiopyrones have been reported to react with phosphoryl or thionyl chlorides to give chloro derivatives, chromones may do so. Reaction of the chromone carboxylic acid (88) with thionyl chloride gave the dichloro acid chloride (89), which was converted into 4-chlorocoumarin by pyridine (61JGU523; 63JGU1806; 72JMC865).



3-Chloroisocoumarin reacted by addition with chlorine to give a high yield of 3,3,4-trichloro-3,4-dihydroisocoumarin (73JOU2160).

c. *Benzothiopyrones*. When the dibenzthiopyrone (90) was treated with xenon difluoride in an endeavour to fluorinate it, it was merely oxidized to a mixture of sulfoxide and sulfone (83MI1). Thiocoumarins with electron-donating groups in the benzene ring are readily brominated there. For example, the 6-amino compound gave the 5-bromo derivative. Us-



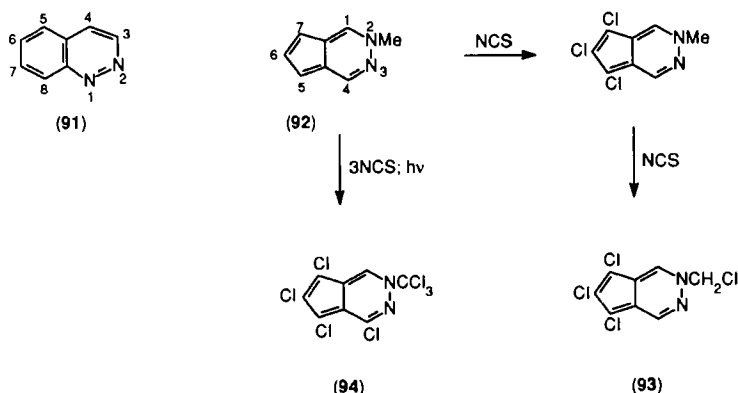
ally, however, the introduction of 5- and 6-bromo groups requires a Sandmeyer reaction. Bromine in chloroform added across the 3,4-bond in thiocoumarin; dehydrobromination in the presence of pyridine led to 3-bromothiocoumarin [80AHC(26)115].

3. Benzopyridazines and Related Compounds

Aspects of the halogenation of benzopyridazines have been discussed in a number of references [73MI2, 73MI3; 74MI2; 79AHC(24)151; 84MI6; 90AHC(47)353]. Molecular orbital calculations predict that cinnoline (91) should react with electrophiles in the regiochemical order $5 = 8 > 6 = 7 > 3 \gg 4$. This order is certainly followed in nitration. It is known that cinnolin-4(1*H*)-one and its 6-chloro, 6-bromo, and 6-nitro derivatives react with sulfonyl chloride or bromine in acetic acid to give the 3-halogeno products, but here the oxygen substituent is exerting the major directional effect. The 5-hydroxy derivative of the same cinnoline, however, reacted with an iodide-iodate mixture to give the 6,8-diiodo derivative; the corresponding 8-hydroxycinnolin-4(1*H*)-one formed the 5,7-diiodo isomer under the same conditions (84MI6).

Moderate yields of the 1- (47%) and 4- (51%) fluoro derivatives of benzo[*c*]cinnoline were obtained by fluorodenitration of the nitro precursors using tetrabutylammonium fluoride. The 2- and 3-fluoro isomers have been made by Schiemann reactions, though yields were only 25 and 35%, respectively (92SC545).

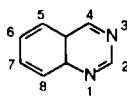
Studies of chlorination and bromination of 2*H*-cyclopenta[*d*]pyridazines (92) have revealed reactivity differences dependent on substituents and halogenation conditions. In monochlorination the unsubstituted compound was more reactive than its 2-methyl and 2-phenyl derivatives, the reactivity ratio being 7.1 : 1.7 : 1 [78H(11)155]. Chlorination occurred most readily in the 5- and 7-positions of the cyclopentadienyl moiety, but once all three positions had been substituted, NCS attacked the methyl group



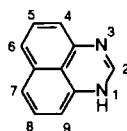
SCHEME 44

to give **93** (80JOC1695). As these compounds are π -excessive analogues of azulene, they should react with electrophiles in the 5-, 7-, and (more slowly) 6-positions with some facility (70T5707; 75JOC2196; 80JOC1695). When the trichloro species was treated with NCS under ultraviolet irradiation, free radical chlorination of the methyl group occurred, but with three molar equivalents of NCS some of **94** was isolated (Scheme 44). Chlorination of the 5,7-dibromo derivative gave 6-chloro product; bromination of the 5,7-dichloro compound also took place in the 6-position (80JOC1695). Treatment of the 1-methyl-2-phenyl derivative with NBS gave a mixture of 5-bromo (27%) and 5,7-dibromo (13%) products (84JOC4769).

4. Benzopyrimidines



(95)



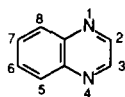
(96)

Those compounds that have no bridgehead nitrogen include quinazoline (benzo[*d*]pyrimidine) (**95**) and perimidine (**96**). Activating groups are needed to effect halogenation. Thus, under vigorous conditions, quinazolin-4(3*H*)-one was converted into a mixture of 6- and 8-mono-, and 6,8-di-chloro products (57JCS2521; 84MI7). Certainly, electrophilic halogenation will not occur readily in the heteroring. As with the pyrimidinones, a detailed study has been made of the mechanism of aqueous bromination of quinazolin-4(3*H*)-one and its 3-methyl derivative. Initial bromination appeared to occur only in the 6-position (no 8-chloro product could be detected), although slow formation of 6,8-dibromoquinazoline was observed. Below pH 2 both substrates exist mainly as cations. The 3-methyl compound was brominated slightly more than unsubstituted quinazolin-4(3*H*)-one, with the pathways believed to involved bromine attack on covalent hydrates (76JOC838).

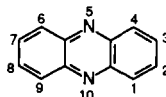
Halogenation of **96** occurs at positions *ortho* and *para* in the naphthalene system, (4-, 6-, 7-, 9-) as donor effects from the nitrogens operate (81RCR816). Thus, one molar equivalent of *N*-chlorobenzotriazole converted perimidine into a mixture of 4- and 9-chloro, and 4,9-dichloro products; 2 mol of chlorinating agent gave mainly 4,9-dichloroperimidine, and this could be further chlorinated to form 4,7,9-tri- and 4,6,7,9-tetra-

chloroperimidine. One mole of sulfonyl chloride in acetic acid, however, gave an 8 : 1 ratio of 6(7)- and 4(9)-monochloro products. Apparent discrepancies between the two reagents can be explained by involvement of the cation with sulfonyl chloride, and the free base with *N*-chlorobenzotriazole (77CL1441; 78CHE788).

Quinazolin-4(3*H*)-one was converted into 4-chloroquinazoline on heating with a mixture of phosphoryl chloride and phosphorus pentachloride [80IJC(B)775]. Phosphoryl chloride in the presence of triethylamine, however, transformed quinazolin-2,4(1*H*,3*H*)-dione into 2-chloro-4-diethylaminoquinazoline. More bulky amines allowed formation of the 2,4-dichloro derivative (82CPB1947).



(96a)



(97)

5. Benzopyrazines

Compounds considered include phenoxazine (96a) and phenazine (97). Electrophilic halogenation should occur more readily than in pyrazine if the analogy with quinoline and pyridine is taken. Calculations for quinoxaline indicate that electron density is highest in the 5- and 8-positions (57JCS2521), and although nitration has been shown to occur to a limited extent at the 5- and 6-positions, direct halogenation of quinoxaline has been synthetically unproductive. 2-Methylquinoxaline gave only the tri-bromomethyl derivative when treated in acetic acid solution with bromine and sodium acetate. With NBS, too, side-chain bromination of this substrate was favored (84MI8).

The presence of strongly electron-donating substituents makes halogenation much more facile. Substitution regiochemistry is largely in accord with simple valence-bond predictions, but the nature of the reactive species (free base or conjugate acid) is also important. Chlorination of the quinoxaline free base gave the 6-chloro derivatives of some 2-hydroxyquinoxalines (as the tautomeric quinoxalinones) in good yields. 2(1*H*)-Quinoxalinone itself gave 60% of 6-chloro-2-hydroxyquinoxaline along with a small amount of the 7-chloro isomer [89JAP(K)01/075474]. An earlier report had claimed a 90% yield of the 7-chloro derivative (63MI1). In 95% sulfuric acid substitution was exclusively at C-6 for both chlorination and iodination (with iodine monochloride). The latter process was accompanied by some N-oxidation (84CL323). The 2,3-dione (98) and its 1,4-

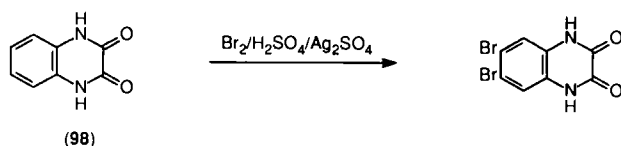
dimethyl derivative were transformed into the 6,7-dibromo derivatives by bromine-sulfuric acid-silver sulfate (62JCS1170) (Scheme 45).

The classical approach to the preparation of chloro- or bromo-quinoxalines is by the action of phosphoryl halides or similar reagents on quinoxalinones (82MI3). These conditions allow introduction of a single chlorine or polychlorination (74MI2). Good yields of chloroquinoxalines have been obtained using phosphoryl chloride in dimethylformamide (80CPB3537; 81CPB2871), or a mixture of phosphoryl chloride and phosphorus pentachloride provided that water was excluded from the workup procedure [the chlorinated products are very prone to hydrolysis (88BSB919)]. A 66% yield of 2,3-dichloroquinoxaline was obtained in this way. Thionyl chloride in dimethylformamide has proved a useful alternative (84CL323).

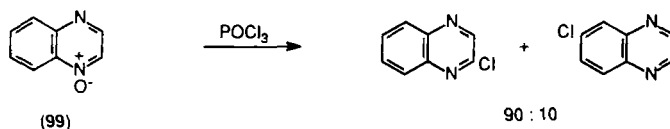
Meisenheimer reaction converts quinoxaline *N*-oxides into chloro-quinoxalines in the usual way. Quinoxaline 1-oxide (**99**) gave 2-chloroquinoxaline and a little of the 6-isomer (67YZ942). That no 5-chloroquinoxaline was observed is surprising since naphthalene-type compounds usually favor α - over β -substitution. The attack of chloride is mainly *ortho* to the *N*-oxide function, but also *quasi-para* to that group (Scheme 46). When the 2- and 3-positions were blocked by phenyl substituents, reaction took place only reluctantly unless carried out in dilute solution with only small amounts of phosphoryl chloride present. The products were the 5- and 6-chloro derivatives in a 1 : 4 ratio. Perhaps coordination of the annular nitrogen with the phosphorus reagent may be hindering 5-chlorination, or 5-chlorination may be exclusively intramolecular, whereas the 6-chloro derivative is a consequence of both inter- and intramolecular routes (87T4329).

Nucleophilic halogen exchange, using cesium fluoride and 18-crown-6 in tetrahydrofuran, gave high yields of 2-, 3-, and 2,3-difluoroquinoxalines from the chloro analogues [87H(26)1215]. The Balz-Schiemann process has been used successfully to make 2-fluoroquinoxaline (84MI8).

Both 2-chloro- and 2,6-dichloro-quinoxalines can be made by ring expansion of 1-methylimidazole using trichloromethyl radicals (91MI5).

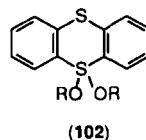
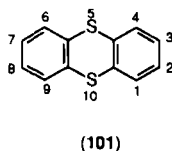
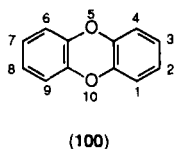


SCHEME 45



SCHEME 46

With phenazine (**97**) there is considerable resistance to any electrophilic halogenation, but in aqueous solution chlorine converted it into a mixture of 1-chloro-, 1,4-dichloro-, 1,4,6-trichloro-, and 1,4,6,9-tetrachloro-phenazines (53G327).



6. Benz Derivatives of Rings with More Than One Oxygen or Sulfur Atom

These derivatives are usually most reactive in the fused heteroring (84MI14).

Benzodioxins are also rather unstable in the presence of electrophiles, but conditions for the successful bromination of dibenzo[*b,e*][1,4]dioxin (**100**) have been described (57JA1439). The corresponding benzodithiins and dibenzo[*b,e*][1,4]dithiin (**101**) readily 2-halogenated. The products of bromination are not always stable and can dehydrobrominate with subsequent formation of polymers (54JA1068). Bromination of **100** gave a mixture of 2,7- and 2,8-dibromo isomers, whereas the 2-nitro derivative of **100** formed the 7-bromo-2-nitro compound (58JA366). Thianthrene (**101**) was reported to react with chlorine at first to give an adduct at sulfur that subsequently rearranged to give the 2-chloro derivative [66HC(21-2)1155]. Bromination gave dibromo products analogous to those observed from **100**, whereas the same mixture of products was obtained on bromination of thianthrene 5-oxide; the sulfoxide group is reduced during the reaction. In contrast, the 5,5-dioxide and 5,5,10-trioxide proved to be inert in the presence of bromine, presumably because there is too much electron withdrawal by the sulfone species (58JOC313). Bromine in alcoholic solution converted **101** into the sulfolane (**102**). This process was probably

initiated by S-bromination followed by oxidation. Frequently 5,10-dioxides are formed in chlorination and bromination sequences [81JCS(P2)382; 90AHC(48)301].

Exhaustive chlorination of **101** gave a mixture of polychloro derivatives with the 2,3,7,8-tetrachloro species as the major product. To achieve such C-halogenation it is necessary to choose a reaction medium that avoids hydrolysis of the initially formed S-halides to S-oxides [76USP3989715; 90AHC(48)301]. The 1-halogenated derivatives of **100** and **101** can be readily prepared from the lithiated species (84MI14).

1,4-Benzoxathiin formed a stable addition product with bromine (54JA1068).

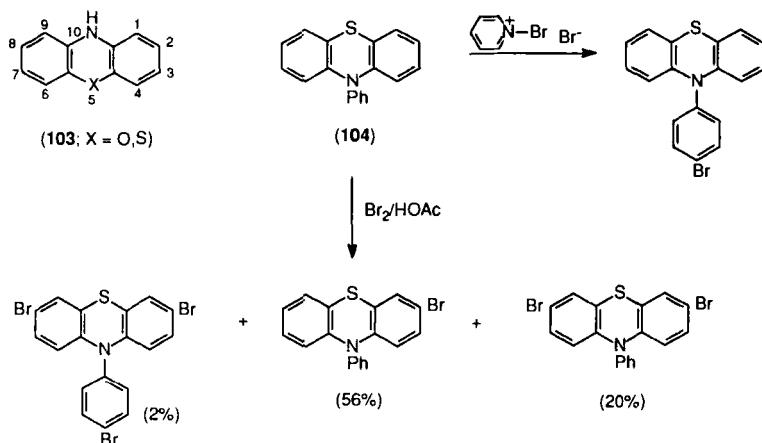
7. Benz Derivatives of Rings with Oxygen or Sulfur and One or More Nitrogen Atoms

Direct bromination of phenoxazine (**103**; X = O) gave rise to a mixture of 3-bromo- and 3,7-dibromo-phenoxazine. Reaction with thionyl chloride gave the 1,3,7,9-tetrachloro derivative (60JGU1872).

Much more is known about the sulfur analogues, especially the benz derivatives of 1,4-thiazine. Bromination of 4*H*-1,4-benzothiazine 1,1-dioxide occurred in the 2-position (68TL1041).

Although it is comparatively unreactive toward many electrophilic reagents, phenothiazine (**103**; X = S) halogenates so readily that it is difficult to prepare monohalogenated derivatives. Chlorine in dimethyl sulfoxide gave the 3,7-dichloro derivative; copper(II) chloride led to the 1,7-dichloro isomer (76JPR353). In nitrobenzene molecular chlorine converted phenothiazine into a tetrachloro-phenothiazine, and ultimately into an octachloro-phenothiazine, in 50% yield [68AHC(9)321; 74MI2]. An activating group in one of the fused benzene rings induces halogenation *ortho* or *para* to that substituent. For example, treatment of 3*H*-phenothiazin-3-one under radical conditions with NBS gave the 4-bromo derivative in 89% yield (85PHA194).

When 10-phenylphenothiazine (**104**) (and 10-phenylphenoxazine) was brominated in acetic acid a number of products were isolated. Pyridine perbromide, though, only brominated the phenyl substituent (Scheme 47). The suggestion that acetic acid bromination might involve the radical cation of the substrate (**104**) was confirmed by generating the radical cation of the substrate (**104**) with perchloric acid prior to bromination. Again a 43% yield of the 3-bromo product and multiple bromination products were observed (Scheme 47). The reaction of 10-phenylphenoxazine with pyridine perbromide appeared to be at least partially electrophilic; the products

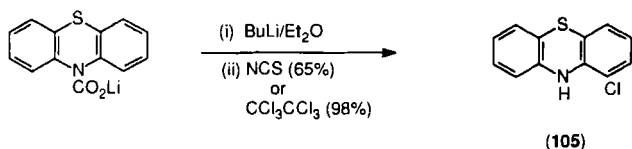


SCHEME 47

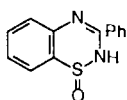
included 3-bromo- (19%), 3,7-dibromo- (11%), 10-(*p*-bromophenyl)- (10%), and 3-bromo-10-(*p*-bromophenyl)-phenoxazine (3%) (84JOC1905).

Halogenations with copper(II) chloride or bromide are also believed to proceed via a radical cation. Such bromination of **104** gave only the 1-bromo derivative, whereas chlorination resulted in the formation of both 1- and 3-chloro isomers (82JPR769). Halogen-metal exchange has proved valuable for the synthesis of 1-chloro- and 1-bromo-phenothiazines (83SC467) (Scheme 48). When protected as its carbamate lithium salt, exclusive lithiation in the 1-position allowed preparation of the 1-chloro derivative (**105**) in high yield (88S215). Similar quenching of the lithium species with 1,2-dibromoethane gave 1-bromophenothiazine (74%) (83SC467).

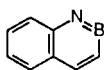
3-Chloro-4*H*-1,2,4-benzothiadiazine 1,1-dioxides have been made from the oxo or hydroxy derivatives [90AHC(50)256; 91CHE343]. Reaction of 2*H*-1,2,4-benzothiadiazine 1-oxides (**106**) with chlorine formed the S-chloro products [90AHC(50)256].



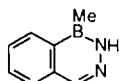
SCHEME 48



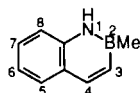
(106)



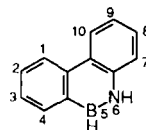
(107)



(108)



(109)



(110)

8. Benz Derivatives of Azaborines

Benzo-fused 1,2-azaborines (**107**) (usually the 1,2-dihydro derivatives) have received some attention [75ACS(B)461; 75ACS(B)1036; 76MI2; 84MI1]. 1,2-Dihydro-1-methylbenzo[*d*][1,2,3]diazaborine (**108**) was brominated at C-4 in preference to the homocyclic ring (66ACS1448). Both bromination and chlorination of 1,2-dihydro-2-methylbenz[*e*][1,2]azaborine (**109**) occurred in the 3-position (84MI1), and the dibenzo derivative (**110**) reacted so readily with halogens that monochloro and monobromo derivatives could not be isolated. Chlorination gave a 60% yield of the 2,4-dichloro derivative; bromination led to 80% of the corresponding dibromide. Trichlorination of the 5-hydroxy derivative occurred in the 2-, 4-, and 8-positions (84MI1).

D. COMPOUNDS WITH ONE SIX- AND ONE FIVE-MEMBERED HETEROAROMATIC RING

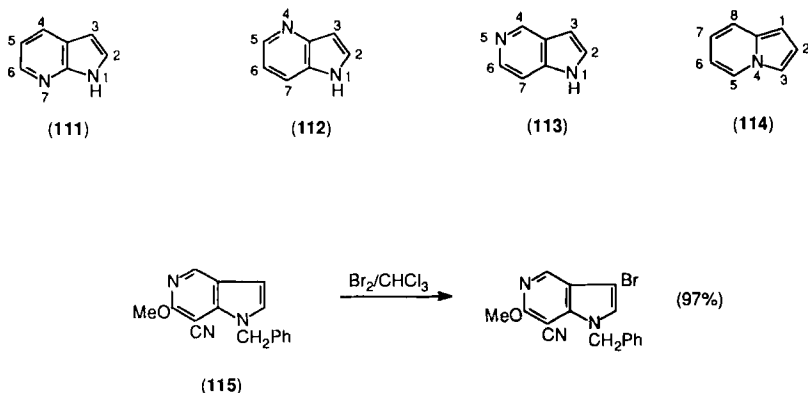
1. Pyridine Fused to a Five-Membered Heterocycle

a. *Pyrrolopyridines*. Compounds considered are **111–114**, and some benz-derivatives (84MI16, 84MI17) (Scheme 49). Pyrrolo[2,3-*b*]pyridine (**111**) reacted with bromine at 0°C in chloroform solution to give the 3-bromo derivative [68AHC(9)27]. The *N*-oxide of **111** was chlorinated at C-4 by phosphoryl chloride [74JCS(P1)2270]. However, direct 6-chlorination and bromination are possible via the Reissert–Henze salt. Yields lie in the range 57–66%. When trichloroacetyl chloride was used as the acid halide, a mixture of 6- (28%) and 4- (32%) chloro isomers resulted. The

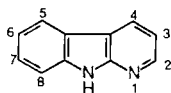
6-iodo-1-methoxycarbonyl derivative was made in 27% yield through reaction of the oxide with trimethylsilyl iodide and HMDS, followed by addition of methyl chloroformate (92S661). The 2,5-dimethyl derivative of the isomer (**112**) was also readily brominated at C-3 in a variety of solvents (65JOU2072). The *c*-fused isomer (**113**) again reacted at the 3-position. Thus, 1-benzyl-6-methoxypyrrolo[3,2-*c*]pyridine-7-nitrile (**115**) gave a high yield of the 3-bromo product despite the deactivating effect of the nitrile function (82CHE268) (Scheme 49).

When there is a nitrogen at the ring junction, as in pyrrolo[1,2-*a*]pyridine (indolizine; **114**), electron withdrawal by the ring nitrogen directs attack to the 1-position, which is about 10^3 times more reactive than the 3-position [71MI3; 90AHC(47)181]. Iodination of 1-acetyl-2-methylindolizine in the presence of sodium acetate gave the 3-iodo derivative (69YZ1020). Regio-specific lithiation of 2-phenylindolizine offers a source of 5-functionalized compounds, although 5-halogenated derivatives do not appear to have yet been made in this way (92TL4433).

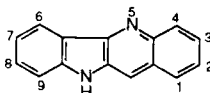
A number of indolopyridines (**116–118**) which have no free pyrrole ring positions can still be halogenated in the fused benzene ring in positions *para* to the *NH* function. Pyrido[2,3-*b*]indoles (α -carboline; **116**) were iodinated by iodine in the 6-position (84CHE345). Similarly, bromine in carbon tetrachloride converted indolo[3,2-*b*]quinoline (**117**) into the 7-bromo derivative in 68% yield (89MI1, 89MI2). A variety of electrophiles (including sources of Cl^+ and Br^+ in acidic media) attacked the protonated species of 7,12-dihydropyrido[3,2-*b*:5,4-*b'*]diindole (**118**) with high selectivity at C-10, thereby differentiating between the two fused benzene rings. With NBS in dichloromethane–trifluoroacetic acid, a 73% yield of the 1-bromo derivative was obtained, along with about 7% of the 3,10-dibromo



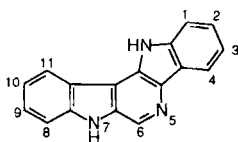
SCHEME 49



(116)



(117)

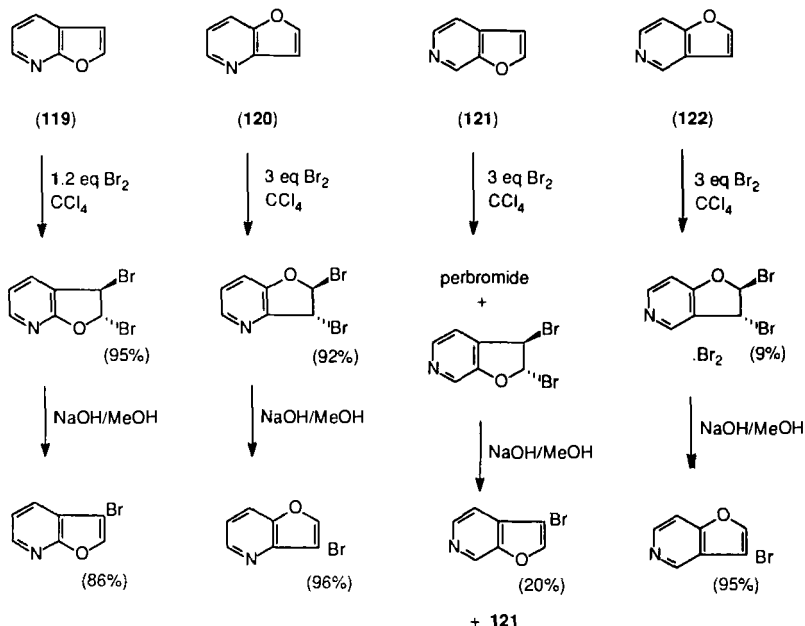


(118)

product. The yield of the latter was raised to 96% by using 2 mol of NBS. When the neutral molecule of **118** was treated with bromine–acetic acid–sodium acetate, however, mixtures of 3- and 10-bromo and polybromo derivatives were formed. Chlorination under acidic conditions proved less successful, but use of excess NCS gave the 3,10- (30%) and 1,10- (21%) dichloro derivatives (88JOC4185).

b. *Furopyridines*. These compounds have been studied in sufficient detail to be able to compare their reactivities [84H(21)738, 84JHC725, 84MI19; 86JHC1465]. Whereas nitrations give mainly 2-nitro derivatives (as with benzofuran), bromination tends to result in addition, thus resembling benzofuran rather than the corresponding thienopyridines (see D,1,c). The considerable double-bond character in the furan rings of **119–122** is evident (84JHC725) (Scheme 50). With 1.2 molar equivalents of bromine, furo[2,3-*b*]pyridine (**119**) gave the *trans*-addition product in high yield. The same molar ratio of bromine to heterocycle seemed to generate only perbromides with **120–122**, but 3 mol of bromine gave the corresponding *trans*-dibromo derivatives, although not always in high yields. Dehydrobromination was virtually quantitative in the formation of the 3-bromofuropyridines (84JHC725). Thus, 74–95% yields of 3-bromo products were obtained when 2-phenylthiofuro[2,3-*b*]-, -[2,3-*c*]-, -[3,2-*b*]-, and -[3,2-*c*]-pyridines were treated with bromine in dichloromethane (92JHC413).

c. *Thienopyridines*. Compared with the analogous furo compounds (**119–122**) thienopyridines are difficult to halogenate [84H(21)738, 84JHC725, 84MI19; 86JHC1465]. Nevertheless, 3-chloro, 3-bromo, and 3-

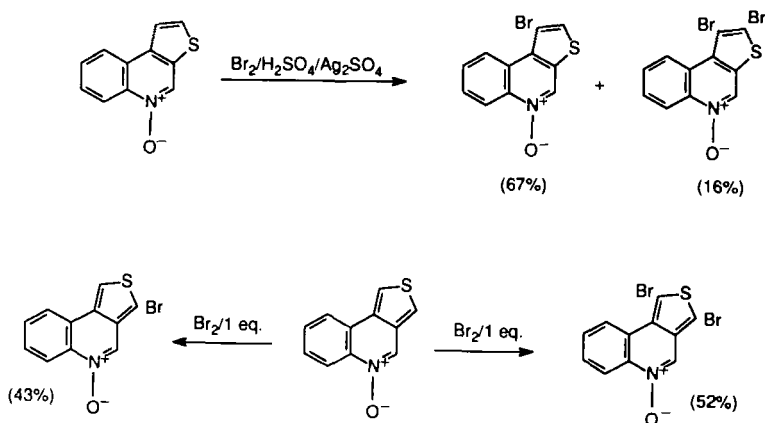


SCHEME 50

iodo derivatives can be prepared using the appropriate halogen in sulfuric acid with silver sulfate (84JHC725). When there are activating groups present, reactivity increases. The bromine–acetic acid–sodium acetate system converted 4-hydroxythieno[2,3-*b*]pyridine into the 5-bromo and then the 2,5-dibromo product with excess reagent. The isomeric thieno[3,2-*b*]pyridin-7(4*H*)-one behaved similarly, initially introducing a bromine adjacent to the oxygen function, and then in the thiophene α -position [80JCR(S)6; 86JCR(S)122].



Variable results have been reported for the halogenation of thieno[2,3-*b*]quinoline (**123**). Initial attack was mainly at the 3-position, but it was difficult to avoid the formation of 2,3-dihalogenated products, even when only 1 mol of halogen was used (predictions are for 2- and 3-substitution [77ZN(B)1331]). Bromine buffered in chloroform gave the 3-monobromo derivative, but analogous chlorination gave a mixture that included some

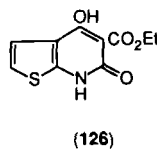
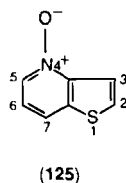


2,3,5,8-tetrachloro product. Some addition across the 2,3-bond and oxidation also occurred; e.g., iodobenzene dichloride converted **123** into **124** [80JCR(S)201]. The *N*-oxides of thieno[2,3-*c*]- and thieno[3,4-*c*]quinoline were also brominated exclusively in the thiophene ring (89CS309) (Scheme 51).

Thieno[4,5-*c*]isoquinoline formed the 2,3-dibromo product in 60% yield, whereas the [3,4-*c*] isomer decomposed under the same conditions (89CS309). Thieno[3,2-*f*]quinoline was brominated in 57% yield at C-2 [70JCS(C)2334].

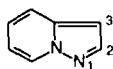
The 2-halogeno derivatives of thieno[3,2-*b*]pyridine are accessible through the lithium derivatives (84JHC785).

Nucleophilic halogenations tend to favor the pyridine moiety. The Meisenheimer reaction of thieno[3,2-*b*]pyridine *N*-oxide (**125**) gave only a 24% yield of a 1.4 : 1 mixture of the 5- and 7-chloro derivatives. Nucleophilic displacement of a 7-nitro group provided a more satisfactory route to the 7-chloro (73%) and 7-bromo (39%) derivatives (85JHC1249).

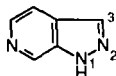


Reports of examples of replacement of an oxo or hydroxy group with chlorine are confined to reactions of the pyridine ring. The [2,3-*b*]thienopyridine (**126**) gave the 5,7-dichloro derivative when treated with dichloro-

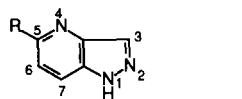
phenylphosphine oxide. That the carbethoxy group is important was demonstrated by the observation that a mixture of 7-chloro and 5,7-dichloro derivatives was formed in its absence [85JCR(S)214]. Reagents like dichlorophenylphosphine oxide, phosphoryl chloride, and phosphoryl bromide have been used successfully with a range of 5- and 7-“hydroxy” [2,3-*b*]- and [3,2-*b*]-thienopyridines [80JCR(S)6; 82JCR(S)158; 86JCR(S)122].



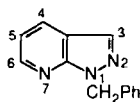
(127)



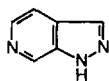
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(129)



(130)

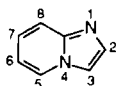


(131)

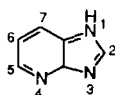
d. *Pyrazolopyridines*. Although halogenation of pyrazolo[4,3-*c*]pyridines has not been reported, isomeric species react in the 3-position as with pyrrolopyridines [84AHC(36)343] (see D,1,a). Thus the [1,5-*a*] compound (127) reacted with bromine in aqueous solution, methanolic bromine in the presence of sodium acetate, or iodine-potassium iodide to give the 3-halogeno derivative in 80, 60, and 63% yields, respectively (65JHC410; 67CHE837) and other examples exist (92CPB639). A 60% yield of the 3-bromo product also resulted when pyrazolo[3,4-*c*]pyridine (128) was treated with bromine water [80JCS(P1)2398]. Both the 5-methyl- and the 5-hydroxy-pyrazolo[4,3-*b*]pyridines (129) gave 97 and 63% yields of their respective 3-bromo derivatives; at higher temperatures the latter product was converted into the 3,6-dibromo derivative (54%) [73JCS(P1)2901]. 1-Benzylpyrazolo[3,4-*b*]pyridine (130) and its 7-oxide gave only low yields of 3-halogenated products when treated with NBS or chlorine in carbon tetrachloride [80JCS(P1)938], whereas the [3,4-*c*] isomer (131) was chlorinated at the 3-position (40%) by sodium hypochlorite [80JCS(P1)2398].

Conversions of diazonium salts into halogenated derivatives have been reported for compounds of type 128 and 129 [73JCS(P1)2901; 80JCS(P1)2398]. Although some 7-substituted pyrazolo[1,5-*a*]pyridines have been made from the lithiated precursors, no halogeno products have been reported (92JOC5538).

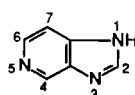
e. *Imidazopyridines*. Species referred to here include imidazo[1,2-*a*]pyridine (**132**; azaindolizine) and the [4,5-*b*] (**133**) and [4,5-*c*] (**134**) isomers. A recent summary of reactions of these compounds has appeared (84MI24).



(132)



(133)



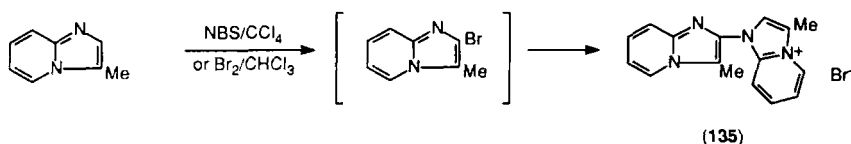
(134)

A kinetic study of the bromination of **132** has demonstrated that attack takes place at the 3-position of the neutral species, and it is 2000 times faster than C-5 attack in imidazole (74AJC2349). Aqueous bromine, bromine in acetic acid, NBS, NCS, and iodine all gave 3-halogeno products (65JOC4081, 65JOC4085; 71JHC37; 77KFZ64; 92JHC691). Even when there was a furan (or thiophene) ring attached to the 2-position of **132**, the initial bromination site was unchanged, although variation of reaction conditions, reagents, or other substituents can change the reactivity to favor furan substitution (65BAU1391; 72CHE627). Only when the 3-position is blocked does initial halogenation occur in the fused pyridine ring [77HC(30)117, 77HC(30)179]. Products of apparent nucleophilic substitution (e.g., **135**) have been identified for the 3-methyl derivative of **132** (80JOC3738) (Scheme 52). The 1- and 3-methyl derivatives of imidazo[4,5-*b*]pyridine (**133**) were brominated in the 6-position (68CHE692; 71CHE256).

Electrophilic bromination (and nitration) of pyrido[1,2-*a*]benzimidazole (analogous to **132**) cannot take place in the imidazole moiety. Initial substitution, using NBS as reagent, was shown to occur at the 8-position, and subsequently at C-4 and C-6 (90JOU1166).

A useful method of synthesis of 5-bromo- and 5,8-dibromo-3-methoxy-2-phenylimidazo[1,2-*a*]pyridines has involved quenching the lithium derivatives with bromine (83S987).

Nucleophilic halogenation procedures include Meisenheimer chlorination of the appropriate *N*-oxides. The 1-methyl 4-oxide of **133** gave a



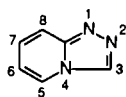
(135)

SCHEME 52

mixture of 5- and 7-chloro products, with the latter being in major yield despite steric hindrance (82JHC513). Similar treatment of 4-oxides of **133** substituted at N-1 by a sugar residue still gave mainly 7-chloro products (82MI1). Whereas 3- β -D-ribofuranosylimidazo[4,5-*c*]pyridine 5-oxide was chlorinated as expected in the 4-position, the reaction failed with the 1-substituted isomer (64JOC2611). The 5-oxide of the parent **134** reacted normally to give its 4-chloride (64CPB866).

Phosphoryl chloride converted imidazo[4,5-*c*]pyridin-4(5*H*)-one into the 4-chloro derivative (65JMC708), and there are other examples of "hydroxy" displacement in the [4,5-*b*] series (58AP368; 70CHE1073).

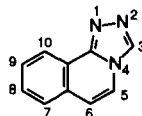
Both 5- and 7-amino derivatives of **133** were diazotized and converted into the chloro derivatives using concentrated hydrochloric acid with or without copper(I) chloride (72RTC650; 78JHC839). Similarly prepared from 4-aminoimidazo[4,5-*c*]pyridine was the 4-chloro derivative (65JMC708). A nitro group in the 4-position of **134** was particularly susceptible to nucleophilic displacement by halide (74CHE744).



(136)



(137)

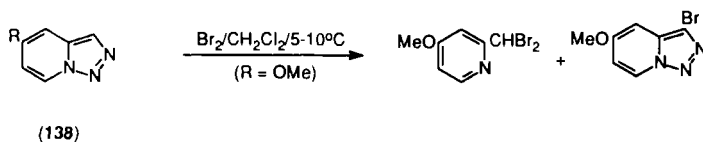


(139)

f. *Triazolopyridines*. Structures discussed here include [1,2,4]triazolo[4,3-*a*]pyridine (**136**), [1,2,4]triazolo[1,5-*a*]pyridine (**137**), and [1,2,3]triazolo[1,5-*a*]pyridine (**138**; R = H).

Bromination of **136** in methanol gave the 3-bromo derivative, identical with the product of Sandmeyer reaction of the 3-diazonium salt. When the reactive 3-position was blocked, electrophilic bromination would not take place (66JOC265). Chlorination appears to occur by addition [83AHC(34)79], and perhalides are known [84MI25; 90AHC(47)1]. Activating substituents are able to induce some bromination in the pyridine ring.

The analogous [1,2,4]triazolo[3,4-*a*]isoquinoline (**139**) was also brominated mainly in the 3-position by a variety of reagents (71CB3925; 74MI3). Chlorine, though, added across the 5,6-bond (71CB3925); the 3-chloro derivative could be prepared using sodium hypochlorite. The 3-chloro and 3-bromo derivatives of **139** have also been made by means of standard diazonium salt transformations, or by heating the 3-hydroxy derivative with the appropriate phosphoryl halide (70JIC894; 71CB3925). The 3-iodo analogue is available from the lithium precursor (71CB3940). Direct



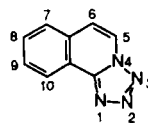
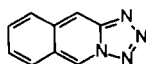
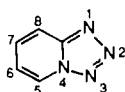
SCHEME 53

lithiation of **139** unexpectedly gave the 5-lithio derivative from which the 5-bromo compound has been made (71CB3965).

The common hydroxylic chlorinating agents were not particularly successful in transforming the 3-hydroxy derivative of **136** into its 3-chloro derivative. Yields with phosphoryl chloride and dimethylaniline only reached 15% (66JOC265).

It was not possible to brominate the [1,2,4]triazolo[1,5-*a*]pyridine species (**137**) directly with bromine or NBS, but the 5- and 8-bromo (66CPB523) and 3-chloro (66JOC265) derivatives were made from the diazonium salts. More recently regiospecific 5-lithiation of **137** has provided access to the 5-bromo derivative in 94% yield (92JOC5538).

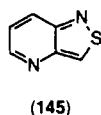
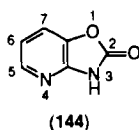
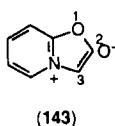
Exposure of **138** (R = OMe) to halogenating agents resulted mainly in ring-opening [81JCS(P1)78; 83AHC(34)79, 83JCR(S)144] (Scheme 53). At 40°C the 7-lithio derivative of **138** readily gave rise to the 7-bromo derivative, but at higher temperatures the triazole ring was opened to form 2-bromo-6-dibromomethylpyridine [82JCS(P1)967, 82JCS(P1)1251; 87JCS(P1)1865].



g. *Tetrazolopyridines*. Bromination of tetrazolo[1,5-*a*]pyridine (**140**) occurred in the 6-position (71T5121; 84MI25). In tetrazolo[1,5-*b*]isoquinoline (**141**), ring-opening accompanied bromination to give 3-azido-4-bromoisouquinoline. It may be that the azido tautomer was the reactive species (81JOC843). The isomeric [1,5-*a*] compound (**142**) has considerable alkene character in its 5,6-bond, and metal exchange reactions at C-5 offer potential for the introduction of halogens at that site (75CB3780).

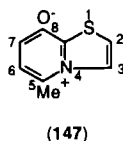
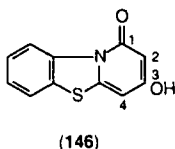
h. *Isoxazolo- and Oxazolo-pyridines*. It is usually essential to have activating substituents present before halogenation is possible. The mesoi-

onic compound (**143**) was rapidly substituted at the 3-position, whereas the oxazolone (**144**), which has no vacant carbon site in the oxazole ring, brominated *meta* to the pyridine nitrogen (at C-6) (76HCA1593; 84MI29). Heating with phenylphosphonic dichloride converted 4,6-dihydroxy-3-methyloxazolo[4,5-*c*]pyridine into its 4,6-dichloro derivative [75JCS(P1)2190].



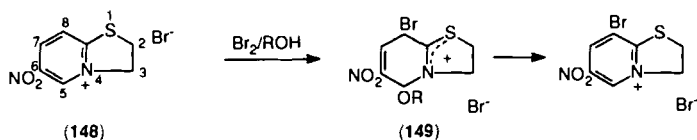
Treatment of 2-phenyloxazolo[4,5-*b*]pyridine and its [5,4-*b*] isomer with LDA followed by quenching with 1,2-dibromoethane gave 53% yields of the isomeric 7-bromo products (92S842).

i. *Isothiazolo- and Thiazolo-pyridines.* Again electron-donating substituents are necessary, and bromine is only successfully introduced into the isothiazole ring of **145** by reaction of the diazonium salt with HBr [79H(12)485; 84MI29].



Bromination of the thiazolo[2,1-*b*]pyridine (**146**) gave the 4-bromo derivative, whereas thionyl chloride 2-chlorinated the heterocycle (88PS251). The 5-methyl derivative of the mesoionic [3,2-*a*] compound (**147**) formed the 7-bromo compound exclusively, but when there was no 5-substituent, both 5- and 7-positions became subject to halogenation. The thiazole moiety was not affected [77ACS(B)919]. Halogens or nitro groups in any azine position subject to nucleophilic attack (e.g., the 7-position of **147**) may be displaced by a halide nucleophile [81H(15)1349]. A 2-thiol group attached to a thiazolonaphthyridine has been replaced by chlorine using sulfuryl chloride (79CPB410).

Studies of halogenation of the partially reduced systems (e.g., **148**) have shown that the 6- (**148**) or 8-nitro-2,3-dihydrothiazolo[3,2-*a*]pyridinium bromides were brominated in hydroxylic solvents with a regiochemistry and ease of reaction consistent with the intermediacy of a pseudo base



SCHEME 54

(149) [81H(15)1349] (Scheme 54). A number of mesoionic systems related to **148** have been chlorinated and brominated (73JHC487).

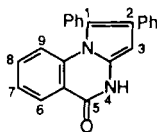
2. Pyrimidine Fused to a Five-Membered Heterocycle

a. *Pyrrolopyrimidines*. Any electrophilic halogenations of these compounds tend to occur preferentially in the pyrrole moiety (69JHC207; 84MI17). Bromine in carbon tetrachloride converted 2-methylpyrrolo[1,2-*a*]quinoxalin-5(6*H*)-one into the 3-bromo derivative [81JMC1455; 86AHC(39)281], whereas the cyanopyrrolo[2,3-*d*]pyrimidine (**150**) was 6-brominated by bromine water [75JCS(P1)1253]. Conversion of the 4,5-dihydropyrrolo[1,2-*a*]quinazolin-5-one (**151**) into the 5-chloro derivative occurred normally with phosphoryl chloride, but phosphorus pentachloride also chlorinated the 3-position [82H(19)249].

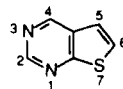


(150)

(R = β -D-ribofuranosyl)



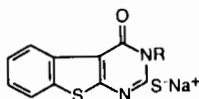
(151)



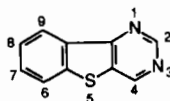
(152)

b. *Thienopyrimidines*. Most is known about the [2,3-*d*] compounds (**152**), which resemble the corresponding pyrrolo- and furo-pyrimidines by being most prone to electrophilic attack in the 5- and 6-positions [68CR(C)(267)697]. Any nucleophilic halogenation will occur in the pyrimidine ring. Unless that position is blocked halogenation occurs first in the β -(5-)position of the fused thiophene ring (84MI19). Thus, 4-hydroxy-5-substituted thieno[2,3-*d*]pyrimidines and their 2,4(1*H*,3*H*)-diones reacted with chlorine or bromine in acetic acid to give the 6-halogeno derivatives (85RCR450; 90JHC717). Bromination of the sodium salts of the thieno[2,3-*d*]pyrimidinones (**153**) and their N- and S-substituted derivatives was ac-

accompanied by the formation of disulfides, which were inert to electrophilic reagents (85CHE1091). At room temperature bromine converted [1]benzo-thieno[3,2-*d*]pyrimidine (**154**) and its 4(3*H*)-one into the 8-bromo deriva-



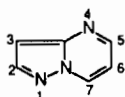
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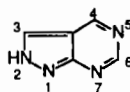
(154)

tive. The oxo compound was the more reactive of the two. Chlorination was similar, but iodination did not take place (72T3277; 80JHC1399).

An oxo group at the 2- or 4-position of **152** can be replaced by chlorine or bromine with the usual reagents and conditions (70BSF3630; 80JHC1399; 85RCR450; 92PHA20).



(155)



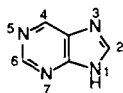
(156)

c. *Pyrazolopyrimidines*. A review of the chemistry of these compounds has appeared recently [87AHC(41)320]. Compounds considered include pyrazolo[1,5-*a*]- (**155**) and pyrazolo[3,4-*d*]- (**156**) pyrimidines.

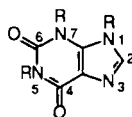
Monobromination of **155** has proved difficult; usually a mixture of 3-bromo and 3,6-dibromo derivatives are formed (75CJC119; 83AP697). The 3-chloro, 3-bromo, and 3-iodo derivatives of the 5,7-dimethyl analogue of **155** were made by direct substitution (74JMC645; 77JMC386). When the 3-position is blocked it is possible to prepare 6-bromo derivatives in good yield. A 7-hydroxy function was readily replaced by chlorine on heating with phosphoryl chloride and dimethylaniline (85AJC221).

In the isomer (**156**) (and its 4-amino and 4-oxo derivatives) 3-bromination also occurred [82CHE753; 87AHC(41)320]. The 4-bromo compound was made in 40% yield from the diazonium salt (82CHE753), whereas a 3-oxo function was replaced by chlorine in the usual way [92JCS(P1)239].

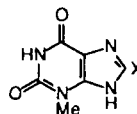
d. *Imidazopyrimidines*. The most common example is purine (imidazo[5,4-*d*]pyrimidine; **157**). Numbering of this compound will follow the order of **157** rather than the traditional (but unsystematic) alternative, which allocates numbers 1- and 3- to the azine nitrogens. Aspects of purine halogenation have been discussed recently [84MI23; 90AHC(47)1].



(157)



(158)



(159)

Both electrophilic and nucleophilic reactions can generate halogenopurines with differences in regioselectivity dependent on substituents and on the nature of the substrate (anion, neutral molecule, or cation). In the neutral molecule nucleophilic displacements occur in the order $2 > 4 > 6$; in the anion the imidazole ring may be sufficiently π -excessive for attack to occur at C-2, and the nucleophilic substitution order becomes $4 > 6 > 2$. Strong electron donors are usually necessary to promote 2-halogenation by electrophilic halogen sources.

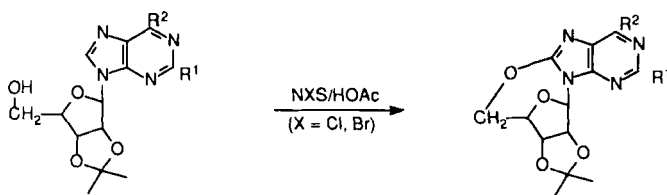
Purine (157) only formed an unstable adduct with bromine, but the 4-amino derivative (adenine) brominated in the 2-position. Solvent effects are important: nonpolar solvents such as chloroform promote 2-substitution, whereas acetic acid can lead to products that are a consequence of addition at the ring junction. Xanthines (158; 4,6-di-“hydroxy” purines) exhibit such behavior [1882LA(215)316; 10CB3553; 14LA(406)22; 17LA(413)155; 28CB1409; 60JGU3306; 64JGU1127].

The use of *m*-chloroperbenzoic acid and HCl in an aprotic solvent was reported for preparing 2-chloropurine nucleosides (81JOC2819).

Bromination is often much faster than chlorination, and although 1,5-dimethylxanthines were only slowly converted into the 2-chloro derivatives by sulfuryl chloride (60JGU3306; 64JGU1127), purines with two activating groups were very rapidly brominated [1883LA(221)336; 63JOC2310]. Even purines with only a single activating group (e.g., adenine) can be 2-brominated with some facility [1890CB225]. Purine nucleosides and their protected derivatives have commonly been brominated at C-2 with reagents like *N*-bromoacetamide and molecular bromine in a variety of solvents (64JA1242).

With hydrobromic acid and potassium bromate 7-methylxanthine (159; X = H) gave the 2-bromo derivative (159; X = Br) in 83% yield (84CHE924). Conversion of a variety of 2-substituted-6-trifluoromethylpurines into the anions, followed by treatment with NBS in hot dimethylformamide, gave 20–60% yields of 2-bromo derivatives (90JHC1505).

Although purine nucleosides can frequently be halogenated at the vacant imidazole carbon (see above), *N*-halogenosuccinimides in acetic acid tend to promote intramolecular cyclizations instead. It has been demonstrated that 2-bromoadenosine is not an intermediate in this process (Scheme 55), which is believed to involve initial attack by positive halogen at N-3.



SCHEME 55

Solvents like dry acetonitrile or dimethylformamide are specific for 2-bromination [88H(27)347].

Most halogenated purines are prepared by replacement of a hydroxy or thiol group (the compounds may exist mainly as the other tautomeric forms) using phosphoryl chloride. The reagent can be used alone, with added phosphorus pentachloride, and with a variety of (frequently tertiary amine) bases. There have, however, been instances in which a dialkyl-amino group was introduced into the purine nucleus when aliphatic amines were used (74RCR1089). Thionyl chloride in dimethylformamide and chloromethylenedimethylammonium chloride in chloroform are also viable alternatives to the phosphorus reagents (64CPB639). When the oxopurines have *N*-alkyl substituents, the enolization process is blocked, and chlorination in these instances may occur with simultaneous elimination of one or more alkyl groups. Concurrent chlorination at a vacant ring position may also be a competing reaction (1897CB2400; 60JGU350; 64JGU2487; 84CHE924; 87JOC1344). When heated with phosphoryl chloride, 2-bromo-7-methylxanthine (**159**; X = Br) had both oxygens and the bromine replaced by chlorine (84CHE924). Amino-oxopurines can also be converted similarly into the chloro derivatives, although guanine was reported to be resistant (1898CB2619; 81CJC2601; 87JOC1344). The 4-bromopurine was prepared in 40% yield by reaction of phosphoryl bromide with hypoxanthine; xanthine, though, only gave a low yield of the 4,6-dibromopurine under similar conditions (56JA3508).

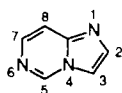
A thioxopurine can often be transformed into a halogenated analogue by reaction with the appropriate halogen. Chlorine in cold ethanol converted 4-thioxo-4,5-dihydropurine into 4-chloropurine, but alcoholic chlorine solutions proved hazardous when used on a large scale. Acetonitrile or hydrochloric acid appear to be safer alternative solvents (74JHC77). 2-Thioxopurines were found to give 2-iodo derivatives when treated with iodine, and methylthiopurines reacted similarly (62JOC986). Perhaps the most valuable aspects of this type of transformation are the mild reaction conditions, which make it applicable to chloropurine nucleoside synthesis, and the fact that it can be used to make 2- and 6-chloro purines, compounds

not so readily available from the corresponding oxopurines (60JA2654; 71MI4).

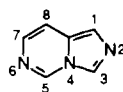
Sandmeyer-type reactions of stable diazonium salts have not been very common routes to halogenated purines (65JA3752; 66JOC3258; 80JOC3969). 6-Amino-4-fluoropurine nucleosides, however, treated sequentially with *t*-butyl nitrite and a 60% solution of HF in pyridine at -20°C gave the 4,6-difluoro products in 48% yield. The 6-chloro and -bromo analogues have been prepared similarly. Yields of the bromo compound were optimized when antimony(III) bromide in dibromomethane was used. Employment of pyridine hydrochloride in dichloromethane as the chloride source gave a 71% yield, raised to 84% by use of antimony(III) chloride in 1,2-dichloroethane (81CJC2608).

Silver fluoride in hot xylene converted 4-chloropurine into the 4-fluoro derivative (63JMC340), whereas similar nucleophilic displacement of a 4-trimethylammonio group by $^{18}\text{F}^-$ formed the labeled 4-fluoro compound under mild conditions (82MI4). In devising nucleophilic schemes for preparing halogenated purines it is useful to be aware of reactivity orders for the unsubstituted [$4 > 6 > 2$ (57JA2185)] and *N*-alkylated species [$2 > 4 > 6$ (63JOC1662)]. Thus 7-methyl-2-nitroxanthine (**159**; $\text{X} = \text{NO}_2$) gave the 2-chloro and 2-bromo derivatives when boiled with the appropriate hydrohalic acid (84CHE924).

Theoretical calculations have predicted that imidazo[1,2-*a*]pyrimidine (**160**) should be attacked at C-3 by electrophiles, although reactivity will be lower than in the corresponding imidazo[1,2-*a*]pyridines (see D,1,e) (74JHC1013). The 3-bromo derivative of **160** was formed when the parent was treated with NBS in chloroform (66JOC809). The usual transformation of oxo to chloro was responsible for the preparation of 5-chloroimidazo[1,2-*a*]pyrimidine [66LA(699)127].



(160)

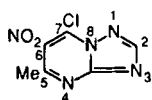


(161)

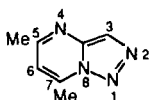
The isomeric imidazo[1,5-*a*]pyrimidine (**161**) gave the 1,3-dibromo derivative when exposed to bromine or NBS (72BSF2481). Iodination of benzimidazo[2,1-*b*]quinazolin-12(5 or 6*H*)-ones was accomplished by boiling them with bromine in the presence of sodium or potassium iodide. Substitution took place at the 9-position in the benzimidazo moiety (91MI3).

e. *Triazolopyrimidines*. Preparation of 7-chloro-[1,2,4]triazolo[1,5-*a*]pyrimidines (**162**) in around 70% yields was achieved by heating the 7-hydroxy compounds with phosphoryl chloride in the presence of dimethylaniline (88EGP255735); other similar processes that give 5- and 7-chloro derivatives have been reported (61CPB801; 63CPB845). Such Vilsmeier conditions have not always proved effective (91ZOR2461). Any electrophilic processes, when possible, tend to favor C-6 (61CPB808; 84MI25).

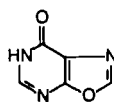
[1,2,4]Triazolo[1,5-*c*]pyrimidin-2-one has been converted into the 2-bromo derivative (65JCS3357), whereas the 5-oxo derivative of [1,2,4]triazolo[1,5-*a*]quinazoline gave the 5-chloro derivative when treated with oxalyl chloride (80HCA1).



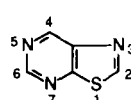
(162)



(163)



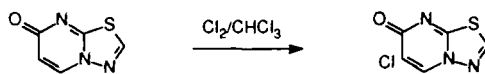
(164)



(165)

Reactions of 5,7-dimethyl-[1,2,3]triazolo[1,5-*a*]pyrimidine (an 8-azapurine) (**163**) with NCS, NBS, or ICl in chloroform failed to produce the 3-halogeno products, leading instead to ring-opened products (76JOC385). Halogen derivatives of [1,2,3]triazolo[4,5-*d*]pyrimidine have been made from the diazonium salts (61JOC4433; 72JMC879) and from the oxo derivatives using rather special reaction conditions [86AHC(39)117]. Thus, conversion of the 5- or 7-amino-[1,2,3]triazolo[4,5-*d*]pyrimidines into diazonium salts allowed preparation of the 5-bromo- and -iodo derivatives (32–65%) and the 7-halogeno derivatives in 41–69% yields. An improved yield (87%) of the 7-iodo derivative was achieved when the chloro analogue was treated with sodium iodide in dimethoxyethane [68JMC513; 82S670; 91CPB2793; 91CPB3037].

f. *Miscellaneous Azolopyrimidines*. (Some data are included in 84MI29.) Phosphoryl chloride converted the oxazolopyrimidine (**164**) into its 4-chloro derivative (71JHC503), and similar reactivity was exhibited by oxo derivatives of some isothiazolo- (70GEP1950990) and thiazolopyrimidine isomers [68CPB750; 71JCS(C)1527; 79JPR260]. Certainly oxo groups in both the 5- and the 6-membered rings of **165** could be replaced by chlorine, although a 2-methylthio group was unaffected [68CPB750; 79JPR260]. Thiazolo[3,2-*a*]pyrimidin-5,7-diones were readily brominated between the two oxygen functions, somewhat resembling the reactivity of mesoionic compounds like **147** (73JHC487).

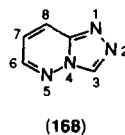
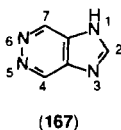
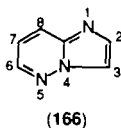


SCHEME 56

When π -deficient thiadiazoles are fused to an azine, electrophilic substitution is possible only in the presence of strongly electron-donating substituents (74BCJ2813) (Scheme 56). Some [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-ones were brominated next to the oxo group (90DOK743).

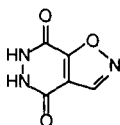
3. Other Azines Fused to a Five-Membered Ring

a. *Pyridazine Fused to a Five-Membered Ring.* Fused pyrazolopyridazines are brominated at any vacant pyrazole site [82JHC817; 83AP697; 90AHC(48)223]. In acetic acid imidazo[1,2-*b*]pyridazines (**166**) were first 3-brominated before conversion by excess bromine into complexes that proved to be useful brominating agents themselves (67T387; 68T239; 81S987). Perchlorination of **166** was achieved at elevated temperatures; milder reaction conditions gave lower chlorinated derivatives in the order $3 > 2, 7 > 8 > 6$ (72M1624; 74M12). The [4,5-*d*] isomer (**167**) is really only prone to nucleophilic substitution reactions. Its 4,7-dichloro compound is typically made from the 4,7-dioxo precursor, although the reaction with phosphoryl chloride has been reported as unsuccessful unless the imidazole moiety is 1-substituted (58JA6083; 68JHC13).

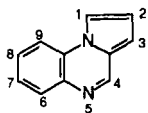


Bromine in acetic acid converted [1,2,4]triazolo[4,3-*b*]pyridazine (**168**) into the 3-bromo derivative despite the HMO and CNDO calculations predicting no C-3 activation. An electrostatic potential map of **168**, however, pointed to the possibility of a direct effect from the triazole nitrogen lone pairs, and further indicated that the lowest potential 15 pm above the molecular plane is associated with C-3 (83CB3513). Free radical chlorination of the same bicyclic species followed a stepwise sequence starting from the 3-position ($3 > 8 > 7 > 6$), and eventually giving the perchlorinated derivative (72M1624; 74M11). The corresponding [1,2,4]triazolo[3,4-*a*] phthalazine was also brominated at the vacant triazole ring position by bromine or NBS (69JOC3221), whereas [1,2,4]triazolo[1,5-*b*]pyridazine was resistant to electrophilic halogenation (74M11).

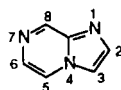
Lactams of type **169** readily gave the 4,7-dichloro derivatives with the usual reagents [75JCS(P1)2190]; the analogous thiadiazolopyridazine reacted in the same way (71MI2; 74MI2).



(169)



(170)



(171)

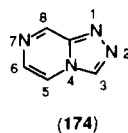
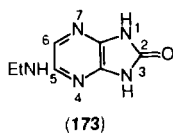
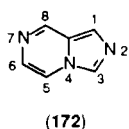
b. *Pyrazine Fused to a Five-Membered Ring.* The calculated reactivity order for electrophilic substitution in pyrrolo[1,2-*a*]quinoxaline (**170**) is $1 > 3 > 6 > 2$ [71JCS(C)2018]. Bromination certainly occurs initially at C-1, but iodination favors the 3-position, possibly for steric reasons [67JCS(C)1164; 68JCS(C)2848]. Indolo[2,3-*b*]quinoxalines reacted with bromine in acetic acid to form the 9-bromo derivatives (substitution in the fused benzene ring *para* to the pyrrole-type nitrogen) (84CHE687).

When thieno[2,3-*b*]pyrazine was chlorinated, the reaction resembled the corresponding pyridine and pyrimidine (**152**) analogues in that β -substitution in the thiophene ring was observed (80JHC1019).

Reaction of thionyl chloride with 1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxalines first introduced a chlorine *para* in the phenyl substituent, and then another into the 2-position (89IJC1026).

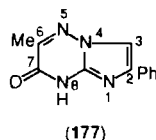
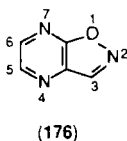
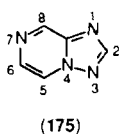
Imidazo[1,2-*a*]pyrazine (**171**) was converted into the 3-bromo derivative by NBS, and into the 3,5-dibromo compound with bromine in acetic acid. The 5-membered ring should be favored by electrophiles, but under severe conditions, and when activating groups are present, the azine ring can also be substituted. Nucleophilic substitutions are always more common in the 6-membered rings, and these processes are accentuated by the fused azole. When **171** was heated at 265°C with phosphorus pentachloride, all five available ring positions were chlorinated (75JHC861; 84MI24).

A mixture of 1- and 3-chloro, 1,3-dichloro, and 1,3,5-trichloro derivatives was obtained on chlorination of imidazo[1,5-*a*]pyrazine (**172**). Bromination gave similar results (75JHC207, 75JOC3373; 84MI24). The 8-chloro compound is best made from the 8-oxy derivative of **172**. When the 1-bromo-3-methyl derivative of **172** was treated in turn with aqueous bromine and excess dilute caustic soda, the pyrazine ring was destroyed to give 4-bromo-2-methylimidazole-5-aldehyde (75JOC3373).



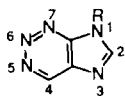
Sufficient activation was present in 5-ethylamino-2-oxoimidazo [4,5-*b*]pyrazine (**173**) for it to be halogenated in the 6-position by chlorine and bromine in acetic acid or by sulfonyl chloride (69FRP1578366; 71BRP1248146). The 2-oxo group could be replaced by chlorine (75KFZ10; 76KFZ35).

In [1,2,4]triazolo[4,3-*a*]pyrazine (**174**) bromination took place at the 5-position rather than in the triazole ring (77JOC4197). It was not possible to convert the 3-hydroxy derivative into the 3-chloro analogue (68JHC485). The isomeric [1,5-*a*] compound (**175**) was also brominated at C-5 (74TL4539), whereas its 7-oxide gave the 8-chloro derivative under Meisenheimer conditions [80JCS(P)506].

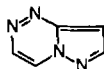


Isoxazolo[4,5-*b*]pyrazine (**176**) is resistant to electrophilic halogenation because the potentially reactive site is at the ring junction. The 7-oxide, though, was converted into the 6-chloro derivative of **176** on heating with phosphoryl chloride (73JHC181).

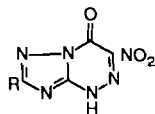
c. *Triazines Fused to a Five-Membered Ring.* Molecular orbital calculations for a number of imidazotriazines have been made (76CHE465). The oxygen function in the imidazo[1,2-*b*][1,2,4]triazine (**177**) was converted into chloro using phosphoryl chloride–phosphorus pentachloride or thionyl chloride in chloroform. The vacant imidazole ring carbon was also subject to a degree of chlorination under either set of conditions (86CHE791). Some 3-bromination of 2,6-diphenylimidazo[1,2-*b*][1,2,4]triazine has also been reported (72JHC1157). The isomeric imidazo[1,5-*b*][1,2,4]triazine was also brominated by NBS in the imidazole ring (52%) (74BSF1453), as was imidazo[1,2-*a*][1,3,5]triazine (70M724). Imidazo[4,5-*d*][1,2,3]triazine (**178**) was chlorinated at C-4 under oxidative conditions (76CHE465).



(178)



(179)



(180)

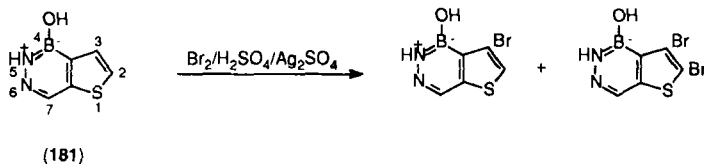
(R = H, Me, Ph)

Bromination of pyrazolo[2,3-*c*][1,2,4]triazines (**179**) occurred only in the pyrazole ring (83AP697).

A variety of halide sources have been shown to be capable of displacing the nitro group of the 1,2,4-triazolo[5,1-*c*][1,2,4] triazines (**180**). Unexpectedly, chlorine and bromine in acetic acid gave the same products, presumably via electrophilic pathways (82CHE992).

d. *Miscellaneous Bicyclic Heterocycles.* Bromination of 4-hydroxy-4,5-borazathieno[2,3-*c*] pyridines (**181**) is dependent on the reaction conditions. With one molar equivalent of bromine in sulfuric acid with added silver sulfate, a mixture of 3-bromo and 2,3-dibromo products was formed. Two molar equivalents of bromine resulted in high yields of the 2,3-dibromo species, but in neutral medium (bromine–carbon tetrachloride–pyridine) selective substitution in the borazapyridine ring was observed [75ACS(B)461; 76MI2] (Scheme 57). The suggestion is that in nonacidic medium there is an addition–elimination pathway similar to that observed for isoquinoline [75ACS(B)461] (see also section C,1,c). Iodination of derivatives of the [3,2-*d*] isomer of **181** with iodine monochloride in pyridine gave the 4-iodo product; bromination in strong acid occurred only in the thiophene ring. Similar halogenation reactivity was also observed in some [4,3-*c*] and [3,2-*c*] isomers [75ACS(B)461].

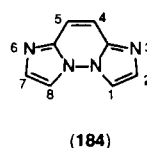
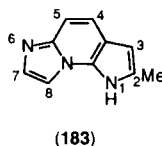
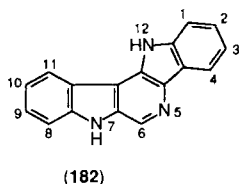
The 1-bromo derivatives were formed in 85–90% yields when 2-methyl (or -phenyl) -4*H*-imidazo[2,1-*c*][1,4]benzoxa (or -benzthia) zines were treated with bromine or NBS in acetic acid. Iodination with NIS or iodine monochloride occurred at C-1 in the imidazole ring in 75–86% yields, but NCS failed to react (92JOC2737).



SCHEME 57

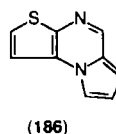
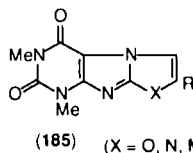
4. Tricyclic Species with One Six- and Two Five-Membered Heterocyclic Rings

The conjugate acid of 7,12-dihydropyrido[3,2-*b*:5',4'-*b*]diindole (**182**) reacted with positive chlorine or bromine with high specificity for the 10-position, effectively differentiating between the two fused benzene rings (88JOC4185). In chloroform the tricyclic compound (**183**) was brominated at C-3 unless that position was blocked by a methyl group. In that eventuality 8-bromination was observed [77JCS(P1)465]. Despite reports of ready nitration in the fused thiophene rings (the *c*-fused ring appears to be the more reactive) of dithieno[3,4-*c*:3',2'-*d*]pyridine and its [2,3-*b*:3',2'-*d*] isomer, no halogenation of these substrates has yet been published (91JHC351).



Although an earlier report (77S761) suggested that diimidazo[1,2-*b*:2',1'-*f*]pyridazine (**184**) was brominated in the 4- and 5-positions, a more recent NMR study has demonstrated that the inherently more likely 1- and 8-positions were substituted (82S1099).

The 3-position of the isoxazole ring was substituted when 2-aryloxazolo[3,2-*f*]xanthines (**185**; X = O) were treated with bromine in acetic acid (90CHE1164). The analogous imidazoxanthines (**185**; X = NMe) also gave 3-bromo derivatives in 75–99% yields (82MI2).

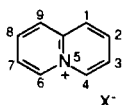


Pyrrolo[1,2-*a*]thieno[2,3-*c*]pyrazine (**186**) brominated mainly in the fused pyrrole ring. Only the third bromine atom introduced substituted the thiophene β -position (86JHC17).

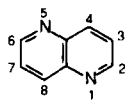
E. COMPOUNDS WITH TWO FUSED SIX-MEMBERED HETEROCYCLIC RINGS

1. *Pyridopyridines*

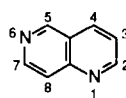
Structures considered are quinolizinium (**187**), and 1,5- (**188**), 1,6- (**189**), 1,7- (**190**), 1,8- (**191**), and 2,7- (**192**) naphthyridines. In the naphthyridines the 10 π -electrons are delocalized in five bonding molecular orbitals, which are distorted by the annular nitrogens in such a way that positions *ortho* and *para* to those nitrogens are less likely to be electrophilically halogenated than *meta* carbons. Compounds with a nitrogen at the ring junction carry a positive charge and will be naturally resistant to electrophilic attack.



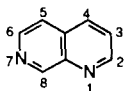
(187)



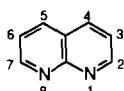
(188)



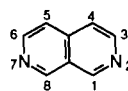
(189)



(190)

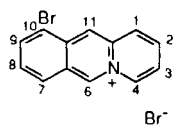


(191)



(192)

a. *Quinolizinium*. Reversible formation of a perbromide resulted when bromine was added to quinolizinium bromide (**187**; X = Br), but heating to 200°C converted the perbromide into a 69% yield of 1-bromoquinolizinium bromide. The corresponding 3-bromo isomer must be prepared by ring synthesis, whereas the 4-isomer has been made from the action of phosphorus tribromide on the 4-quinolizone (the 4-chloro derivative can be made similarly). Both 1,2- and 3,4-dibromo salts were prepared in 65 and 11% yields, respectively, from the 1-bromo-2-hydroxy and 3-bromo-4-oxy substrates [81H(15)213]. Electron-donating groups in the ring accelerate electrophilic halogenation reactions, directing the incoming halogen usually into positions *ortho* and *para* to the substituent (63JCS2203; 64JCS2760; 65JOC526, 65T945; 84MI4). Yields are frequently in the range 50–90%. Quinolizinin-4-one was initially brominated in the 3-position, and then at C-1 (65T945), whereas 2-hydroxyquinolizinium gave the 1-bromo product in 67% yield (64JCS2760).



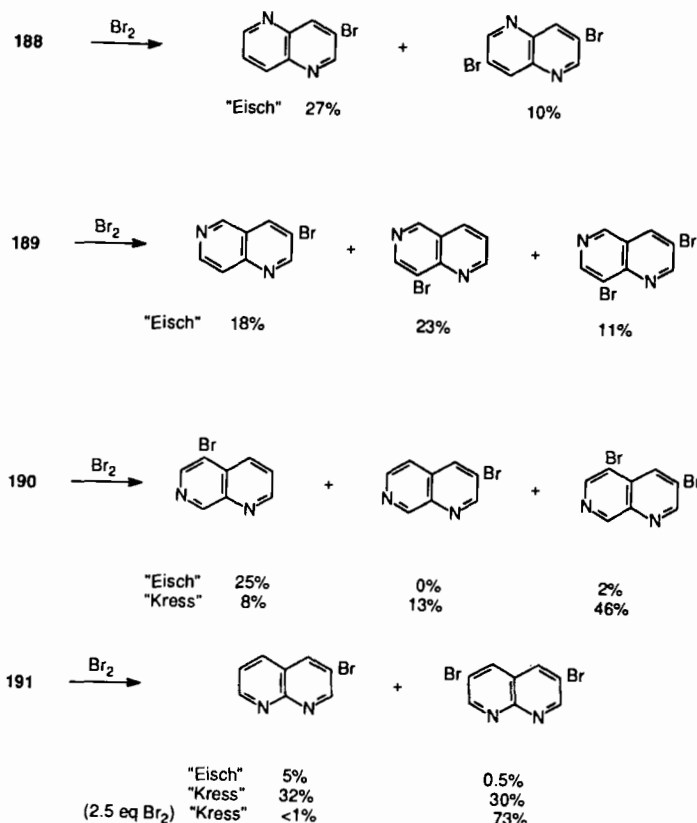
(193)

A fused benzene ring, as in acridizinium (benzo[*b*]quinolizinium), is more susceptible to halogenation than either of the pyridine moieties. Reaction of acridizinium with bromine gave a 7,8,9,10-tetrabromo addition product that eliminated HBr to form 10-bromoacridizinium bromide (**193**). Sulfuryl chloride and aluminium chloride converted the original salt into the 7,10-dichloro derivative (77%) (67JOC1169). At 100°C in the presence of Lewis acids, halogens can be induced to enter the 6- and 11-positions by an ionic mechanism, the details of which are yet uncertain (84M14).

b. *Naphthyridines*. Halogenation properties of the naphthyridines are a composite of those of pyridine, quinoline, and isoquinoline with electrophilic substitution taking place, where possible, β to the ring nitrogens [83AHC(33)147; 84M15; 90AHC(47)1; 92JHC1197].

When 1,5-naphthyridine (**188**) was treated with bromine in fuming sulfuric acid the 3-bromo derivative was obtained in low yield along with some 3,7-dibromo product. Bromination in carbon tetrachloride in the presence of pyridine gave the same products in 27 and 10% yields, respectively [54JCS1879; 63RC1589; 65JOC1607; 67LA(707)242; 68JOC1384]. At 500°C in the gas phase, bromination of **188** gave a mixture of 2-bromo, 2,6-dibromo, 2,3,6-, and 2,4,6-tribromo products, presumably as a consequence of homolytic processes (73RC2123).

The use of bromine in a solvent such as carbon tetrachloride with added pyridine is sometimes known as the Eisch method. An alternative process [Kress method (72USP308389; 73JHC409)] involves treatment of the naphthyridine hydrohalide with bromine in nitrobenzene. Yields and product regiochemistry vary between the two methods, possibly because the former involves a quaternary *N*-bromo compound, and the latter a quaternary *NH* compound. Some typical experimental results are shown in Scheme 58. The low yields obtained from **191** may be a consequence of its complexing properties (68JOC1384), and dibromination of this substrate was shown to take place most efficiently under Kress conditions [72JCS(P1)705; 75FRP2207100]. It is noteworthy that in the Kress procedure the yields are very much affected by the salt used. In the dibromination of 1,7-naphthyridine (**190**) the hydrobromide gave a 46% yield of 3,5-dibromo product; the yield from the hydrochloride was only



SCHEME 58

6.5% (76JHC961). When 2,7-naphthyridine (**192**) was brominated, a mixture of 4-bromo and 4,5-dibromo products was formed (70JHC419). In basic medium bromine converted benzo[*b*][1,8]naphthyridine-9-carboxaldehyde into the 3,7-dibromo-9-carboxylic acid (92JHC1197).

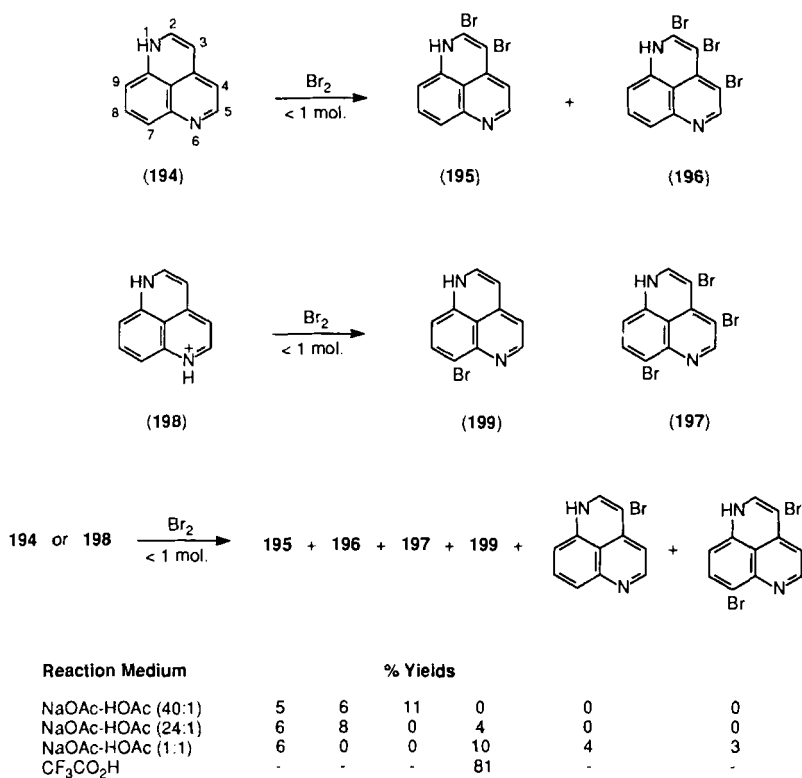
Activating substituents exert their usual effects. Thus, both 1,5-naphthyridin-4-one and the corresponding -2-one were brominated in the 3-position (56JCS212), as was 1,6-naphthyridin-4-one (65JHC393). There are numerous other examples that proceed under milder halogenation conditions than are usually required for the unsubstituted naphthyridines [63JCS4237; 70AHC(11)123; 73RC2361; 74RTC144; 75JOC660, 75M11; 78JHC731; 84MI5; 90AHC(47)1]. An *N*-oxide group is also weakly activating and it may be lost during the process. 1,5-Naphthyridine 1-oxide gave a mixture of 3,6-dibromo-1,5-naphthyridine and its oxide. Additionally a little 3,7-

dibromo-1,5-naphthyridine was isolated, probably as a by-product of bromination of deoxygenated material (75JOC3068). The Meisenheimer reaction of 1,6-naphthyridine 1,6-dioxide has been studied in detail (72JHC1151).

An oxo group in naphthyridine can be replaced by chlorine or bromine with the usual reagents. When heated with phosphoryl bromide or phosphorus pentabromide 1,5-naphthyridin-4-one formed either the 4-bromo or the 3,4,7-tribromo derivatives, depending on the reaction conditions. 1,6-Naphthyridin-4-one gave a mixture of 4-bromo and 4,8-dibromo products with phosphoryl bromide, but phosphorus pentabromide treatment led to the formation of the 3,8-dibromo-4-one and 3,4,8-tribromo-1,6-naphthyridine. Phosphoryl bromide converted 1,8-naphthyridin-2-one into a mixture of 2-bromo and 2,6-dibromo derivatives. It should be noted that the second bromination appears always to take place at the usual site of electrophilic substitution in the parent, unoxxygenated naphthyridine (73RC2361; 74RC1815; 75JOC660; 76JHC43; 79MI1; 84MI5; 85AJC459). When 3-bromo-8-hydroxy-1,5-naphthyridine was refluxed for 10 h with phosphoryl chloride, the 3-bromo-8-chloro derivative formed (85AJC459). Similar reaction of 4,6-dioxoanthyridine with a mixture of phosphoryl chloride and phosphorus pentachloride gave the 4,6-dichloro product (70JHC875).

Fluorinated derivatives of **191** have been prepared from chlorofluoropyridine carboxylic acids (92JMC518).

An extensive study of the bromination properties of the 1,6-diazaphenylene system has been made [81H(16)2125; 82CJC3049]. Bromination of the neutral species (**194**) gave mainly the 2,3-dibromo (**195**) and 2,3,4-tribromo (**196**) derivatives along with smaller quantities of other isomers [e.g., 3,4,7-tribromo (**197**)]. The conjugate acid (**198**) was mainly subject to 7-halogenation, giving **199** (Scheme 59). Certainly the 3-position in the neutral molecule and C-7 in the conjugate acid would be the expected electrophilic bromination sites, but it is necessary to invoke addition-elimination to account for attack at the other positions. With the 2- and 3-positions highly polarized, attack by bromide at C-2 seems logical [81H(16)2125; 82CJC3049]. Calculations of total charge density for **194** predicted an order of preferential electrophilic substitution of $3 > 4 > 9 > 7$. For the cation (**198**) the order is $3(4) > 7(9)$. When HOMO electron densities were calculated (relevant to reactivity with electrophiles) these theoretical reactivity orders became $7 > 3 > 4 > 9$ and $7 > 3$, respectively, for **194** and **198**. The LUMO electron densities, which apply for nucleophilic attack, predicted C-2 and C-5 as the most likely sites (82CJC3049).



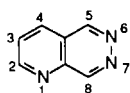
SCHEME 59

Medium effects were found to be important. A decrease in pH favored more 7-bromination, whereas the proportion of **195** remained fairly constant. Product ratios (Scheme 59) show pH dependence similar to that of imidazole bromination (74AJC2331). In acidic media, both NBS and NIS gave mainly 7-halogeno products (65% and 50 yields, respectively), and NCS gave the 7-chloro along with smaller quantities of 3-, 2,3-, and 3,7-chlorinated species (82CJC3049).

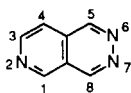
2. Pyridopyridazines

Although electrophilic substitution in these compounds is difficult, bromination of pyridyl[2,3-*d*]pyridazine (**200**) gave a 3-bromo derivative, in accord with charge density calculations [73HC(27)968]. It is likely that this product formed as a result of HBr elimination from a 3,4-dibromo

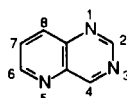
addition compound. Attempted chlorination resulted only in ring-cleavage (69AJC1745). A similar process in the [3,4-*d*] isomer (**201**) gave rise to 8-bromo product (77BSF665). A few other examples of halogenation of the *N*-oxides of pyridyl[2,3-*c*]pyridazine and pyridazino[3,4-*c*]isoquinolines have been reported (72JHC351; 84MI9).



(200)

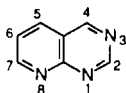


(201)

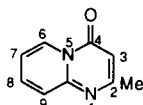


(202)

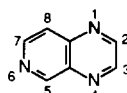
Nucleophilic chlorination in the 3-position was observed when the 5,8-dibromo derivative of **200** was heated strongly with phosphorus pentachloride, a reaction also common to the [3,4-*d*] compounds (72MI1).



(203)



(204)



(205)

3. Pyridopyrimidines

Structures considered include pyrido[3,2-*d*]pyrimidine (**202**), the [2,3-*d*] isomer (**203**), and derivatives (e.g., **204**) of the [1,2-*a*] isomer. Oxo groups are readily replaced by heating with the usual sources of chloride; monochloro compounds are formed under mild conditions, but forcing conditions frequently cause polychlorination (72JHC91; 78CHE1261; 84MI9; 87RCR1140). The 4(3*H*)-one derivative of **202** was converted by oxalyl chloride and dimethylformamide in chloroform into the 4-chloro derivative (98%) (84M1309). A Sandmeyer reaction was used to prepare 2-chloropyrido[3,2-*d*] pyrimidine (91CHE394).

Methyl groups on pyridopyrimidines can be laterally brominated under radical conditions (79JHC133), but when **204** was treated with NBS in the presence of peroxide very little methyl bromination was observed. Instead, the main product in 88–96% yield was the 3-bromo derivative [84IJC(B)1117]. 3-Chlorination of a derivative of **204** has also been reported [83AHC(33)241].

Pyrido[2,1-*b*]quinazolinone (analogous to **204**) and its 2,8-dinitro derivative were brominated by bromine in acetic acid, but the products are of unknown structure. Reaction with a mixture of phosphoryl chloride and

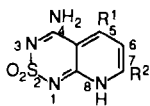
phosphorus pentachloride at 180–190°C gave an undefined trichloro product [86AHC(39)281].

4. *Pyridopyrazines*

True electrophilic bromination of pyrido[3,4-*b*]pyrazines (**205**) only occurs in the presence of activating substituents, e.g., amino groups (70JHC1195; 79JMC862; 84MI9). Rather surprisingly ethyl 3-methylpyrido[3,4-*b*]pyrazine-7-carboxylate gave the 8-bromo derivative rather than the bromomethyl product on treatment with NBS (64JOC734). The 2,3-dimethyl derivative of **205**, however, was laterally brominated, whereas with iodine in pyridine the 2-pyridinomethyl salt was obtained (71ZC256). During reaction of 2,3-dihydroxypyrido[3,4-*b*]pyrazine with phosphorus pentachloride some 7-chlorination was observed (84MI9). 2-Azaquinolizinium *N*-oxides were readily brominated in the 1-position [67JCS(C)2391].

5. *Miscellaneous Bicyclic Heterocycles Based on Pyridine*

Selective bromination of pyrido[2,3-*c*][1,2-*b*]thiadiazine 2,2-dioxides (**206**) gave 6-bromo products in 71–85% yields (91SC827).



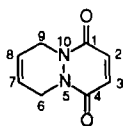
(206)

($R^1, R^2 = \text{H, Me, Ph}$)

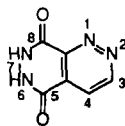


(207)

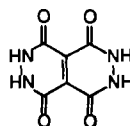
Bromination of 10,10-dimethyl-2-aza-10-silanthrone (**207**) with NBS in acetic acid gave the 4-bromo derivative (30%), whereas in 80% sulfuric acid attack was in the 5- and 7-positions in the fused benzene ring (total yield 45%). Reduced yields in the presence of a radical initiator demonstrated that the reaction in acetic acid was not a homolytic process. The



(208)



(209)



(210)

analogue of **207** with the oxo function missing could not be brominated in acetic acid, and in sulfuric acid the silicon—carbon bond was broken (86JGU2129).

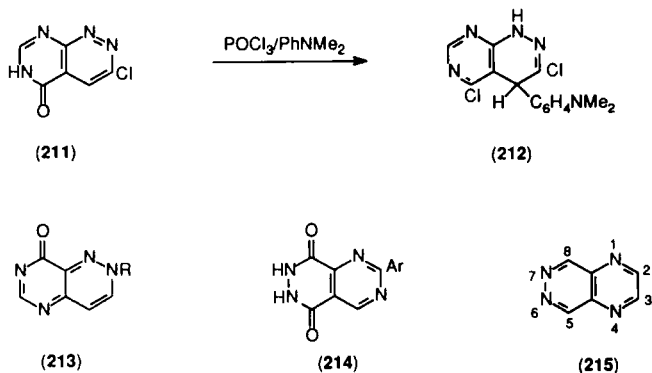
6. Pyridazinopyridazines

Discussion here focuses on the pyridazino[1,2-*a*]pyridazine system (e.g., **208**) and the [4,5-*c*] (**209**) and [4,5-*d*] (e.g., **210**) derivatives (84MI11).

Bromination of **208** at -78°C in dichloromethane gave the 7,8-dibromo addition compound (72TL1885). A further mole of bromine in chloroform at room temperature added to the 2,3-bond (75JOC47). Although **209** and its 3-methyl derivative have been reported resistant to chlorination under standard conditions (67JHC393), the 3-phenyl derivative was converted into the 5,8-dichloro compound when heated with phosphoryl chloride (72YZ1327), and **210** gave the tetrachloro derivative under analogous conditions [72JCS(P1)953].

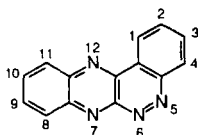
7. Pyridazinopyrimidines

When the pyrimido[4,5-*c*]pyridazine (**211**) was heated with phosphoryl chloride and dimethylaniline **212** was formed (71CPB1849). Some oxo derivatives appear to be resistant to chlorination; e.g., the pyrimido [5,4-*c*]pyridazine derivative (**213**) would not react (68JHC523). 2- Arylpyrimido[4,5-*d*]pyridazines (**214**), however, were readily converted into the 5,8-dichloro derivatives in high yields (72CPB1513; 84MI11).

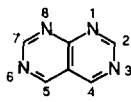


8. *Pyridazinopyrazines*

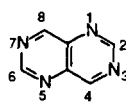
The 5,8-dione of pyrazino[2,3-*d*]pyridazine (**215**) was chlorinated by phosphoryl chloride–phosphorus pentachloride mixtures to give the 5,8-dichloro derivative. Analogous bromination was also achieved. Pyrazino[2,3-*d*]pyridazin-5-one, however, could not be halogenated (69JHC93; 84MI11). Nucleophilic attack by hydrogen halides on quinoxalino[2,3-*c*]cinnolines (**216**) gave 10-halogeno products (or 9-substituted if C-10 was blocked). Yields approached 70–90% for both HCl and HBr (83TL3151).



(216)



(217)



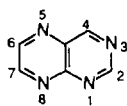
(218)

9. *Pyrimidopyrimidines*

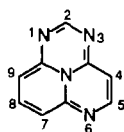
The 4-oxy derivatives of pyrimido[4,5-*d*]pyrimidines (**217**) were readily chlorinated by the usual reagents (62JOC4211; 74JMC451). Hydroxy derivatives of the [5,4-*d*] isomer (**218**) reacted similarly. The 2,4,8-tri- and 2,4,6,8-tetra-chloro derivatives were accessible in this way, and subsequent reaction of these with iodide gave iodochloro derivatives; exchange at the 4- and 8-positions was faster than at C-2 and C-6 [60LA(631)147; 66JMC610].

10. *Pyrimidopyrazines*

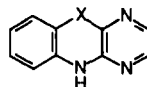
The fused system, pyrimido[4,5-*b*]pyrazine (**219**), is more commonly known as pteridine, a ring system which is present in such biologically important molecules as alloxazine, riboflavin, leucopterin, xanthopterin, and the coenzyme, flavin-adenine dinucleotide.



(219)



(220)



(X = S, Se) (221)

Although the simple mono-(2-,4-,6-, and 7-) and some di-(6,7-, 2,4-) tri-(2,4,6-, 2,4,7-), and tetra-(2,4,6,7-) -chloro derivatives are known, they are often unstable and highly susceptible to nucleophilic attack, and little is known about some of the compounds (64JCS1666; 84MI10). No electrophilic halogenations have yet been reported, but there have been a few instances of chlorine introduction by Meisenheimer reaction of pteridine *N*-oxides (78JOC680; 82LA2135).

11. *Pyrimidotriazines*

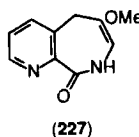
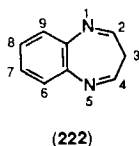
Bromination of 1,3,6-triazacycl[3,3,3]azine (**220**) occurred initially at the 4-position, then at C-7 and C-9, as predicted (73ACS2421). The 4-cyano-3-methyl derivative gave 7- and 9-brominated products (72ACS624). Similar bromination of ethyl 2-methyl-1,3,4,7-tetracycl[3,3,3]azine-9-carboxylate occurred at the 6-position (73ACS2421).

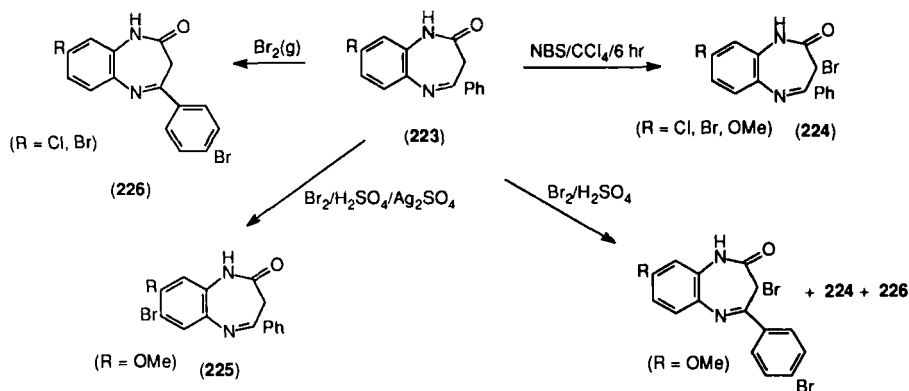
12. *Miscellaneous Bicyclic Heterocycles*

Excess chlorine in acetonitrile converted 1,4-diazaphenothiazine (**221**; X = S) into 2-carboxamidobenzothiazole. The corresponding phenosele-nazine (**221**; X = Se) was ring-opened under the same conditions (80T2681).

F. COMPOUNDS WITH A SIX- AND SEVEN-MEMBERED RING

Although the 1,5-benzodiazepines (**222**) are less reactive with electrophiles than the uncondensed heterocycles, they can be brominated at C-3. Bromination orientation, though, is a function of reagent and substitution pattern. Reactions of some 8-substituted 4-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-ones (**223**) are shown in Scheme 60. Gaseous bromine attacked only the phenyl substituent to give **226**, NBS in carbon tetrachloride 3-brominated the substrate giving **224**, and acidic reagents were much less specific. The formation of the 7-bromo derivative (**225**) depends on the 8-substituent being an electron donor (84CHE927) (Scheme 60).





SCHEME 60

Phosphoryl chloride and dimethylaniline converted the pyridoazepinone (227) into its 9-chloro derivative. The corresponding 7-oxo derivative reacted similarly, but thiones were unaffected [86JCR(S)204].

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